A STUDY OF CAROTID INTIMA-MEDIA THICKNESS AND RETINAL ARTERY CHANGES IN PATIENTS WITH NON ALCOHOLIC FATTY LIVER DISEASE

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CERTIFICATE FROM THE DEAN

This is to certify that this dissertation entitled "**A STUDY OF CAROTID INTIMA-MEDIA THICKNESS AND RETINAL ARTERY CHANGES IN PATIENTS WITH NON ALCOHOLIC FATTY LIVER DISEASE** " is the bonafide work of **DR. PRABHU T M** , in partial fulfillment of the university regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai, for M.D General Medicine, Branch I examination to be held in April 2017.

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DECLARATION

I, **DR. PRABHU T M,** solemnly declare that this dissertation titled "**A STUDY OF CAROTID INTIMA-MEDIA THICKNESS AND RETINAL ARTERY CHANGES IN PATIENTS WITH NON ALCOHOLIC FATTY LIVER DISEASE**" is a bonafide record of work done by me at the Department Of General Medicine, Government Rajaji Hospital, Madurai, under the guidance of **Dr.R. PRABHAKARAN. M.D**, Professor, Department of General Medicine , Madurai Medical college , Madurai.

This dissertation is submitted to The Tamil Nadu Dr. M.G.R Medical University, Chennai in partial fulfillment of the rules and regulations for the award of M.D Degree General Medicine Branch- I; examination to be held in April 2017.

Place: Madurai Dr. PRABHU T M

Date:

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CONTENTS

A STUDY OF CAROTID INTIMA-MEDIA THICKNESS AND RETINAL ARTERY CHANGES IN PATIENTS WITH NON ALCOHOLIC FATTY LIVER DISEASE

INTRODUCTION

Carotid Intima Media Thickness (CIMT) is a useful tool for detection of sub-clinical atherosclerosis. It therefore, not only indirectly indicates the presence of coronary atherosclerosis but also gives some estimation of its severity

Non-Alcoholic Fatty Liver Disease (NAFLD) is one of the most common liver diseases reported all over the world and the disease spectrum ranges from simple steatosis to non-alcoholic steato-hepatitis to cirrhosis

Fatty liver, the common term used for NAFLD has strong association with metabolic syndrome. Obesity, type-2 diabetes, dyslipidemia and insulin resistance is therefore evident in most of these patients . As there is a clear association of fatty liver disease being a part of spectrum of metabolic syndrome, several studies have been conducted to establish NAFLD as an independent risk factor for atherosclerosis and cardiovascular disease

The CIMT is considered to be a non-invasive marker for atherosclerosis and the thickness is directly proportional to the presence of atherosclerosis in the coronary vessels and the severity of cardiovascular disease.

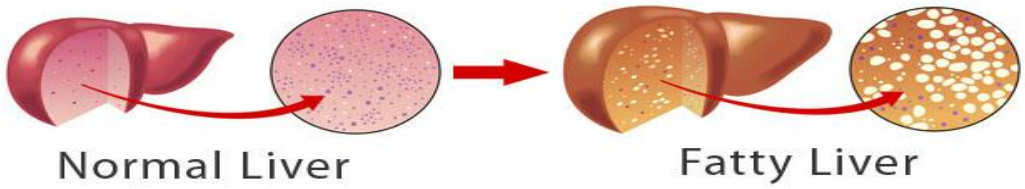
The aim of our study is to determine the relationship between NAFLD and CIMT and retinal artery changes by comparing the CIMT of patients and fundus chages with sonographically proven NAFLD with a group of patients having normal echogenicity of liver parenchyma on ultrasound.

AIMS & OBJECTIVES

1. To measure the thickness of Carotid Intima Media (CIMT) in patients with Non-Alcoholic Fatty Liver Disease (NAFLD) and compare it with Controls, to establish the strong association of NAFLD with increased CIMT and to prove that NAFLD an independent risk factor for cardiovascular morbidity.

2. To look for any associated retinal artery changes in NAFLD**.**

REVIEWOF LITERATURE



NONALCOHOLIC FATTY LIVER DISEASE

Definition

Nonalcoholic fatty liver disease (NAFLD) is one of the most common causes of chronic liver disease. It encompasses a spectrum of conditions associated with lipid deposition in hepatocytes.

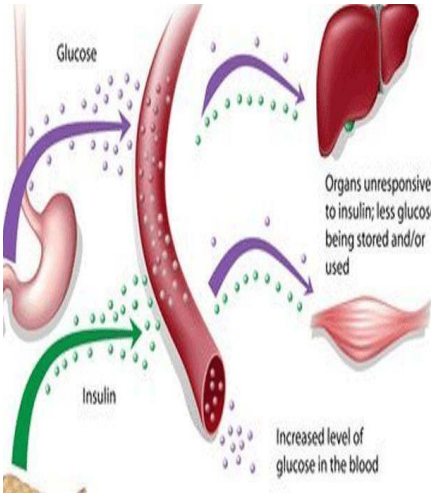
It ranges from

1. steatosis (simple fatty liver),
2. nonalcoholic steatohepatitis (NASH–fatty changes with inflammation and hepatocellular injury or fibrosis),
3. advanced fibrosis and cirrhosis .

Studies suggest that although simple fatty liver is a benign condition, NASH can progress to fibrosis and lead to end-stage liver disease. The

disease is mostly silent and is often discovered through incidentally elevated liver enzyme levels.

It is strongly associated with obesity and insulin resistance and is currently considered by many as the hepatic component of the metabolic syndrome. NASH cirrhosis is now one of the leading indications for liver transplantation in the United States.



Because NAFLD resembles alcoholic liver disease but occurs in people who drink little or no alcohol, excessive daily alcohol consumption must be ruled out before making the diagnosis.

Limit - less than 20gm/day 

10g alcohol = 30ml of whisky = 100 ml of wine = 240 ml of beer

Numerous other conditions leading to fatty liver must be excluded by history, physical examination, and appropriate testing.

Prevalence and Risk Factors

Accurate epidemiologic data are not available because of a lack of population-based studies and reliable noninvasive screening tools. There is disagreement about the methods used to diagnose NASH, and there is no clear consensus on the clinical implications of histologic changes or on the influence of the amount of alcohol ingested.

The prevalence of NAFLD is affected by many factors, including genetics (predilection to alcohol abuse, sex) and environment and is therefore difficult to define. In general, the risk of liver disease increases with the patient's body mass.

Based on the available data, NAFLD is estimated to occur in one-third of the general population in the US. The prevalence of NASH is more difficult to determine. It seems to occur in approximately 3% of the US population but may be found in more than 25% of obese persons.

The prevalence of overweight persons (body mass index [BMI] ≥25 kg/m2) in the US has risen to more than 65%, and obesity (BMI ≥30 kg/m2) is now present in more than 30% of the adult US population.

The prevalence is increased in men, older individuals (those aged 40-70 years), and those with components of the metabolic syndrome especially diabetes and abdominal obesity. The prevalence of childhood obesity and NAFLD is at similar levels. NAFLD has been observed in all ethnic groups with the highest prevalence seen in Hispanics compared with Caucasians and African Americans.

CAUSES

Nonalcoholic fatty liver disease
Excessive alcohol consumption
Drugs Estrogens Coumadin Tamoxifen Valproic acid Methotrexate Isoniazid Corticosteroids Vitamin A Troglitazone l-Asparaginase Amiodarone Perhexiline Calcium channel blockers Nucleoside analogues

Hepatitis C (genotype 3)
Nutritional factors
Rapid weight loss
Total parenteral nutrition
Starvation
Protein-calorie malnutrition
Surgical considerations
Gastrointestinal surgery for obesity
Extensive small-bowel resection
Metabolic disorders
Cystic fibrosis
Abetalipoproteinemia
Others

Syndromes associated with obesity and insulin resistance

Lipodystrophies

Hypopituitarism

Prader-Willi syndrome

Other

Inflammatory bowel disease

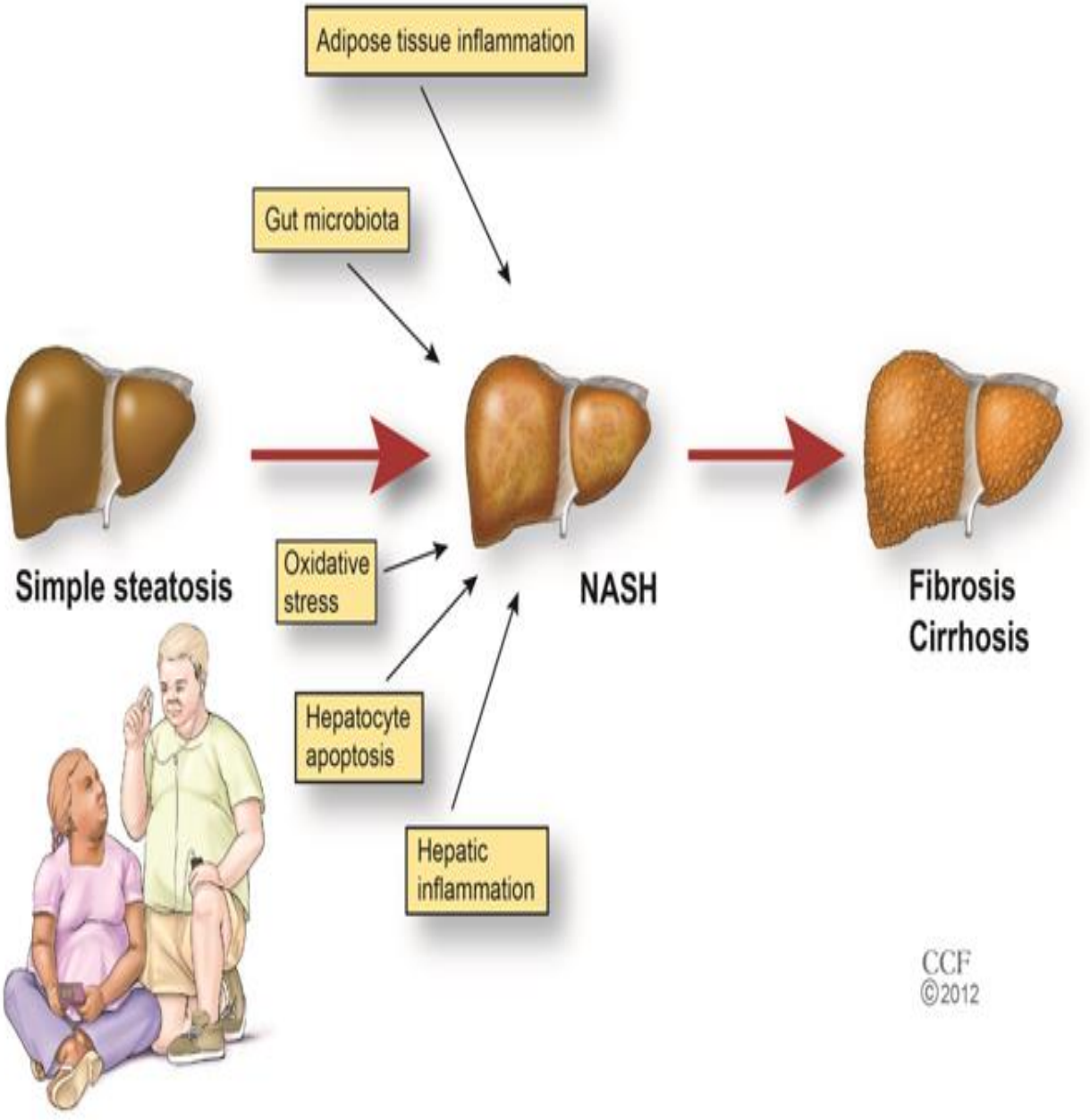
Small-bowel diverticulosis with bacterial overgrowth

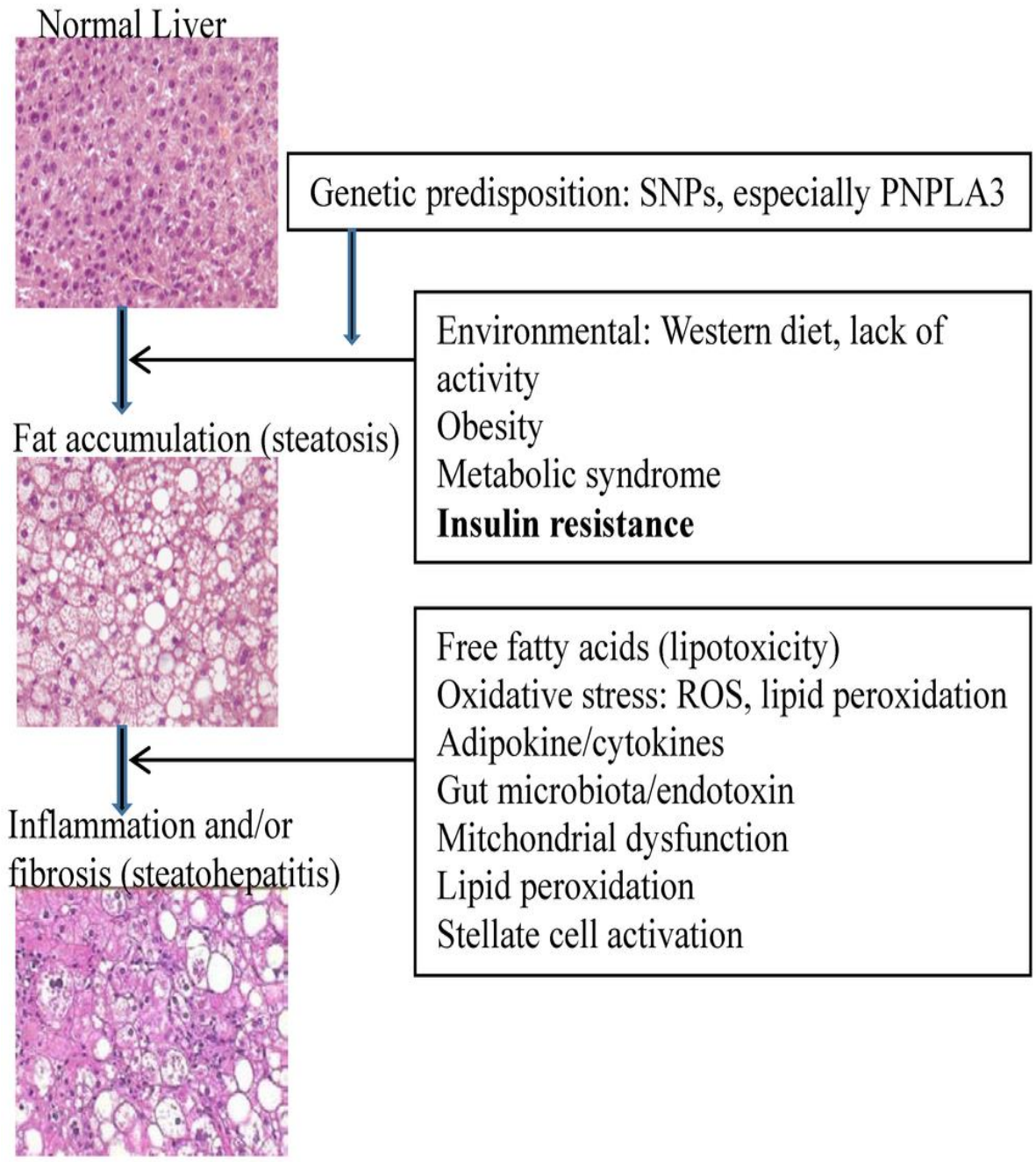
Virus infection

Petrochemicals

Toxic mushrooms

Pathophysiology




NAFLD Progression
Risk factors
Normal Liver
Genetic predisposition: SNPs, especially PNPLA3
Environmental: Western diet, lack of activity
Obesity
Metabolic syndrome
Insulin resistance
Fat accumulation (steatosis)
Free fatty acids (lipotoxicity)
Oxidative stress: ROS, lipid peroxidation
Adipokine/cytokines
Gut microbiota/endotoxin
Mitchondrial dysfunction
Lipid peroxidation
Stellate cell activation
Inflammation and/or fibrosis (steatohepatitis)

Development of NASH may be the result of 2 liver insults.

With the initial insult, **macrovesicular steatosis** occurs which is a manifestation **of excessive triglyceride** accumulation in the liver. Insulin resistance and subsequent hyperinsulinemia appear to lead to alterations in the hepatic pathways of uptake, synthesis, degradation, and secretion of free fatty acids and ultimately to accumulation of lipids in the hepatocytes. These changes seem to make the liver susceptible to a second insult, resulting in an inflammatory response and progression of liver damage. Oxidative stress, mainly caused by mitochondrial dysfunction, and proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-alpha), are believed to play an important role in the progression of liver damage in NAFLD. Potential oxidative stressors include hepatic iron, leptin, antioxidant deficiencies, and intestinal bacteria. Hepatocyte apoptosis, an organized form of cell death, has been identified as a potential key component of the second insult involved in NAFLD progression.

Natural History

Overall, morbidity and mortality have been shown to be significantly higher in NASH patients compared with the general population.

1. Coronary artery disease

2. malignancy

3. liver-related mortality are the most common causes of death in NASH patients.

Children with NASH also have a significantly shorter duration of survival compared with people in the general population.

Data suggest that the natural history of NAFLD is determined by the severity of the histologic damage. Most patients with NAFLD have pure steatosis without inflammation and are reported to have a benign clinical course. Of patients with NASH 15% to 25% progress to cirrhosis and its complications over 10 to 20 years.

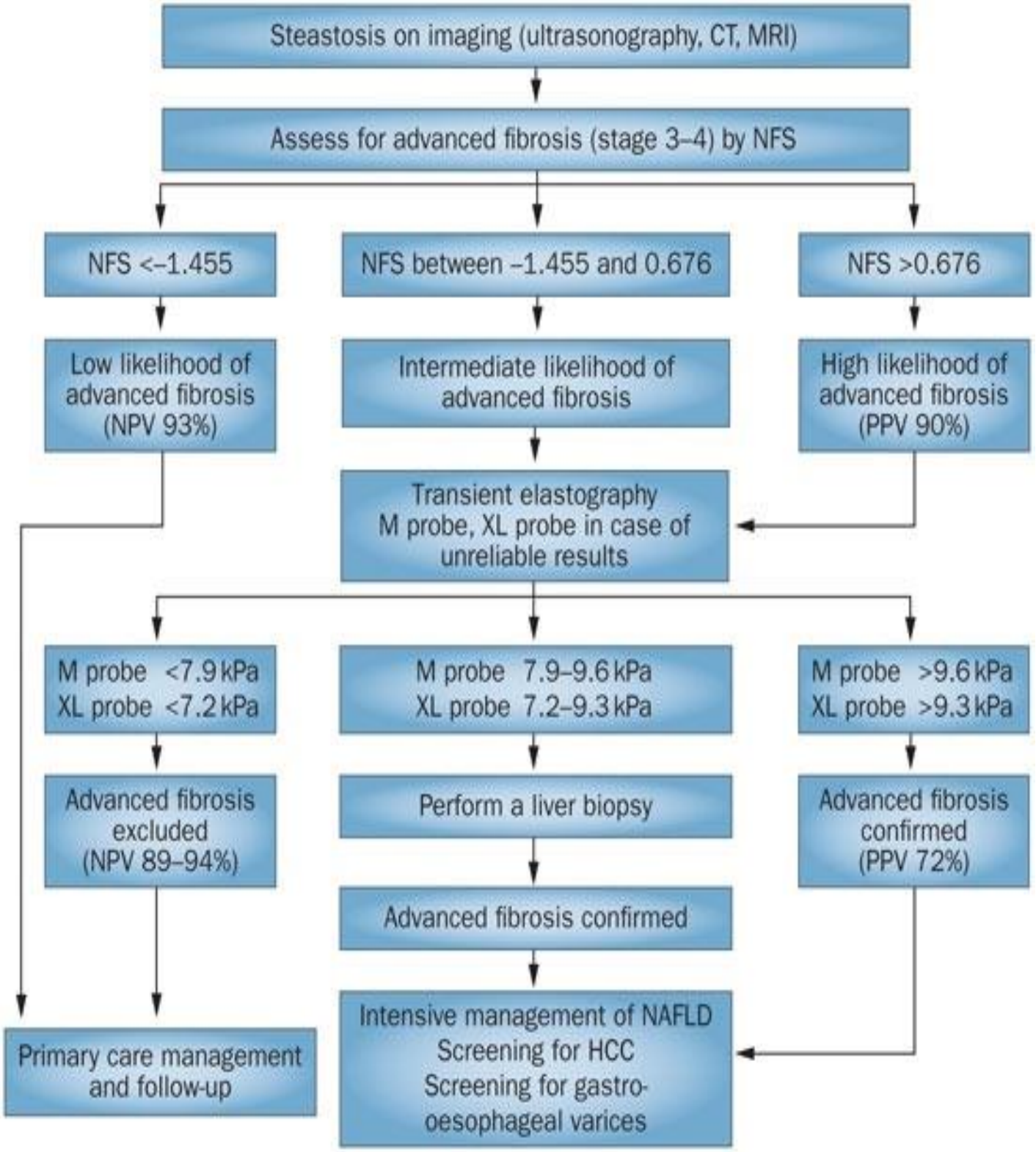
At the time of initial biopsy, as many as one-third of NASH patients have advanced hepatic fibrosis, whereas 10% to 15% have well-established cirrhosis. It is now recognized that a large portion of patients with cryptogenic cirrhosis have burned-out NASH: the histologic feature of steatosis or

steatohepatitis is replaced by a bland cirrhosis. NASH cirrhosis is a risk factor for development of hepatocellular carcinoma (HCC).

Some studies report a prevalence of HCC in NAFLD patients of 0% to 0.5% and 0% to 2.8% in NASH patients over a 20-year period. Data in Japanese patients suggest that the cumulative rate of HCC at 5 years may be as high as 15%. NASH-associated cirrhosis is an increasing indication for liver transplantation. Recurrence after liver transplantation has also been reported as has de novo NAFLD following liver transplantation for other reasons.

Further studies are needed to define the pathogenesis of NAFLD clearly and explain the apparent inter-individual variation in the susceptibility to progress to more-advanced liver disease. Genetic factors have been suggested to play an important role in this variation, and several new candidate genes have been proposed.

	Histologic grades	Ultrasonograghic grades		p-value
		Children of grade 1 and grade 2 fatty liver (%)	Children of grade 3 fatty liver (%)	
NAS[a]	Non-NASH (≤4)	4 (57.1)	1 (9.1)	**0.026**[b]
	NASH(≥5)	3 (42.9)	10 (90.9)	
Steatosis amount	Grade 0 (<5%)	0 (0.0)	0 (0.0)	
	Grade 1 (5-32%)	4 (57.1)	2 (18.2)	**0.046**[b]
	Grade 2 (33-66%)	2 (28.6)	3 (27.3)	
	Grade 3 (>66%)	1 (14.3)	6 (54.5)	
Lobular inflammation	Grade 0 (no foci)	0 (0.0)	0 (0.0)	
	Grade 1 (<2 foci/200x)	3 (42.9)	3 (27.3)	0.28
	Grade 2 (2-4 foci/200x)	4 (57.1)	6 (54.5)	
	Grade 3 (>4 foci/200x)	0 (0.0)	2 (18.2)	
Portal inflammation	Grade 0 (none to minimal)	7 (100)	5 (45.5)	**0.02**[b]
	Grade 1 (greater than minimal)	0 (0.0)	6 (54.5)	
Ballooning degeneration	Grade 0 (none)	0 (0.0)	0 (0.0)	
	Grade 1 (few)	4 (57.1)	1 (9.1)	**0.03**[b]
	Grade 2 (many)	3 (42.9)	10 (90.9)	
Fibrosis	Grade 0 (none)	0 (0.0)	0 (0.0)	
	Grade 1 (zone 3 perisinusoidal)	1 (14.2)	2 (18.2)	
	Grade 2 (perisinusoidal and portal/periportal)	3 (42.9)	1 (9.1)	0.493
	Grade 3 (bridging fibrosis)	3 (42.9)	8 (72.7)	
	Grade 4 (cirrhosis)	0 (0.0)	0 (0.0)	


Steastosis on imaging (ultrasonography, CT, MRI)
Assess for advanced fibrosis (stage 3–4) by NFS
NFS <–1.455
NFS between –1.455 and 0.676
NFS >0.676
Low likelihood of advanced fibrosis (NPV 93%)
Intermediate likelihood of advanced fibrosis
High likelihood of advanced fibrosis (PPV 90%)
Transient elastography M probe, XL probe in case of unreliable results
M probe <7.9 kPa XL probe <7.2 kPa
M probe 7.9–9.6 kPa XL probe 7.2–9.3 kPa
M probe >9.6 kPa XL probe >9.3 kPa
Advanced fibrosis excluded (NPV 89–94%)
Perform a liver biopsy
Advanced fibrosis confirmed (PPV 72%)
Advanced fibrosis confirmed
Primary care management and follow-up
Intensive management of NAFLD Screening for HCC Screening for gastro-oesophageal varices

NASH CLINICAL RESEARCH NETWORK HISTOLOGICAL SCORING SYSTEM

NASH activity grade: grade = total score: S + L + B (range 0–8)

Steatosis	S score	Lobular inflammation	L score	Hepatocyte ballooning	B score
< 5%	0	None	0	None	0
5–33%	1	< 2	1	Few ballooned cells	1
34–66%	2	2–4	2	Many ballooned cells	2
> 66%	3	> 4	3		

NASH fibrosis stage	Stage
None	0
Mild, zone 3 perisinusoidal fibrosis	1a
Moderate, zone 3 perisinusoidal fibrosis	1b
Portal/periportal fibrosis only	1c
Zone 3 perisinusoidal and portal/periportal fibrosis	2
Bridging fibrosis	3
Cirrhosis	4

Signs and Symptoms

Most persons with NAFLD are asymptomatic, and liver disease is often discovered incidentally when laboratory examination shows elevated liver enzyme levels. It is the most common cause of unexplained persistent elevation of liver enzyme levels after hepatitis and other chronic liver diseases have been excluded.

The most common symptoms that bring NAFLD to medical attention are malaise, fatigue, and right upper quadrant or diffuse abdominal discomfort. Hepatomegaly is commonly found on clinical examination. When cirrhosis appears, stigmata of chronic liver disease, such as spider angiomata, ascites, splenomegaly, hard liver border, palmar erythema, or asterixis, can be present. Patients might complain of jaundice or pruritus, or they might present with a complication of portal hypertension (eg, ascites, variceal bleeding, or encephalopathy). Most patients have associated features of the metabolic syndrome (Table 2): obesity (47%-90%), diabetes mellitus (28%-55%), and variable incidences of hyperlipidemia (4%-92%) and hypertension.

Diagnostic criteria for metabolic syndrome

Parameter*	Value
Impaired glucose tolerance	Fasting blood glucose level ≥110 mg/dL
High blood pressure	≥130/85 mm Hg
Elevated triglyceride levels	>250 mg/Dl
Low high-density lipoprotein level	<40 mg/dL for men; <50 mg/dL for women
Abdominal obesity	Waist: >102 cm (40 inches) for men; >88 cm (35 inches) for women

**** Metabolic syndrome is diagnosed by the presence of 2 or more of these parameters.***

Diagnosis

Table III. Modified classification according Brunt

Macrovesicular steatosis grade:
0: No
1: < 33 %
2: 33-66 %
3: > 66 %
Necroinflammatory activity
1: Mild: steatosis < 60 %, few ballooned hepatocytes, few neutrophils ± lymphocytes, little or no portal inflammation
2: Moderate: Steatosis, ballooned hepatocytes abundant, numerous neutrophils, portal inflammation
3: Intense: Panlobular steatosis, ballooning degeneration intense, diffuse infiltration of neutrophils, portal inflammation
Fibrosis stage:
Perisinusoidal or pericellular
Perisinusoidal or pericellular and portal or periportal fibrosis
Perisinusoidal or pericellular fibrosis and portal bridging fibrosis, focal or extensive
Cirrhosis

NAFLD is usually diagnosed during further evaluation for elevated aminotransferase levels found in one of three situations:

1. on routine checkup,
2. when monitoring is performed for possible side effects of drugs (most often cholesterol-lowering medication),
3. for non specific symptoms.

NAFLD can also be identified incidentally on imaging or, less often, on liver biopsy done for other reasons. Some centers screen for NAFLD in high-risk groups that include patients with elements of the metabolic syndrome.

Clinical evaluation includes a careful history and physical examination. It is particularly relevant to inquire about excess alcohol consumption—defined as >30 g/day for men and >20 g/day for women within the past 5 years; 350 mL (12 oz) of beer, 120 mL (4 oz) of wine, and 45 mL (1.5 oz) of hard liquor each contain 10 g of alcohol—and to define the nonalcoholic nature of the condition.

Moreover, it is necessary to exclude the alternative causes of fatty liver. It is most important to include anti-hepatitis C antibody as well as serum ceruloplasmin levels in young patients.

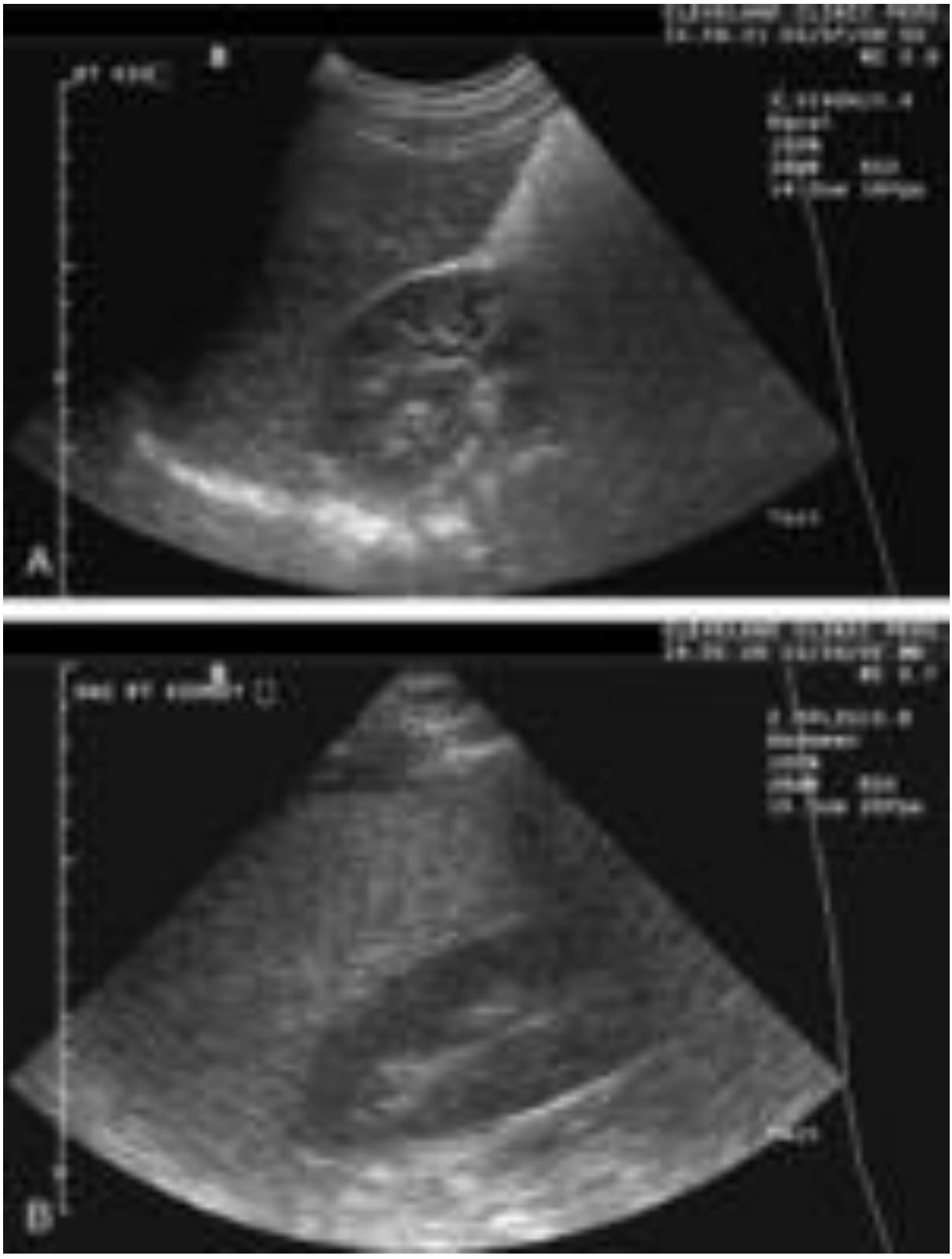
Primary noninvasive evaluation may be used to confirm the diagnosis of fatty liver disease, given the risks and costs of a liver biopsy. Clinical factors and basic laboratory evaluation, particularly in patients aged 45 years and older, or those with obesity, type 2 diabetes mellitus, or an aspartate aminotransferase-to-alanine aminotransferase (AST/ALT) ratio >1, have been shown to be predictors of more-severe histologic disease and may be useful in making a decision regarding when to order a biopsy. Histologic evaluation is the gold standard and should be considered.

Laboratory Evaluation

In a patient with suspected NAFLD or NASH, useful baseline testing should include levels of AST, ALT, total and direct bilirubin, and fasting serum glucose, as well as a lipid panel. Mild to moderate elevation of serum aminotransferase levels is most commonly found (mean range, 100-200 IU/L). Generally, the ratio of AST to ALT is <1, but this ratio increases as fibrosis advances. Liver enzyme levels are normal in a large percentage of patients with NAFLD; normal aminotransaminase levels do not exclude the presence of advanced disease. Serum alkaline phosphatase and g-glutamyl transpeptidase levels may also be mildly abnormal. Given that more than 80% of patients with

NAFLD have some components of metabolic syndrome, serum levels of fasting cholesterol and triglycerides, as well as fasting glucose and insulin, should be determined. Albumin, bilirubin, and platelet levels are usually normal unless the disease has evolved to cirrhosis. Some patients with NAFLD have low titers of autoimmune antibodies (antinuclear and anti–smooth muscle antibody) and an elevation of ferritin. The role of these markers is still unclear.

Imaging

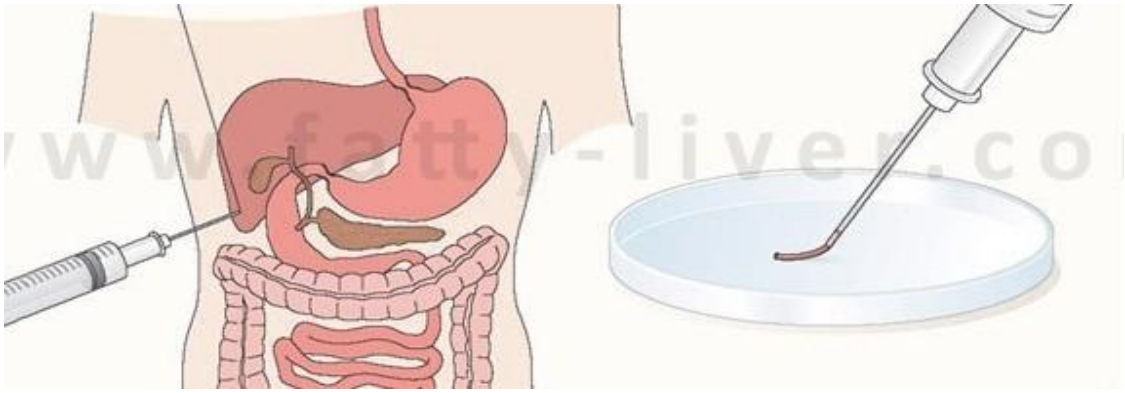


A liver ultrasound examination is useful for confirming steatosis. Fatty infiltration of the liver produces a diffuse increase in echogenicity (a bright liver) and vascular blurring (Figure 2). Unfortunately, ultrasound cannot rule out steatohepatitis or fibrosis, and its sensitivity drops sharply when <30% of hepatocytes contain fat droplets. It also has low accuracy in obese patients. Both computed tomography (CT) and magnetic resonance imaging (MRI) studies, especially the new technique of magnetic resonance spectroscopy, are more sensitive modalities for quantifying steatosis. However, none of these imaging techniques has sufficient sensitivity and specificity for staging the disease and cannot distinguish between simple bland steatosis and NASH with or without fibrosis. Hepatic elastography is a non-invasive measurement of hepatic fibrosis by measuring liver stiffness, which is increased with increased fibrosis. Ultrasound elastography is limited in obese patients. Magnetic resonance elastography has not been shown to detect NAFLD. Elastography is currently not widely available in the US.

Liver Biopsy

Liver biopsy is of unquestioned value in determining the presence of steatosis, distinguishing steatosis from steatohepatitis, and assessing

the degree of fibrosis. Because the diagnostic accuracy of noninvasive diagnostic tools is low, histology is the most reliable means to grade the severity of the disease and thus estimate prognosis. Biopsy is also helpful in ruling out an alternative diagnosis. In addition to establishing the cause and severity of disease, histology permits the monitoring of disease progression and the response to therapy, because aminotransaminase levels can decrease during the course of the disease regardless of whether fibrosis progresses or improves. A histologic scoring system (NAFLD activity score) has been proposed to aid with diagnosis and monitoring of the disease.



NAFLD is histologically indistinguishable from liver damage resulting from alcohol-induced liver injury. The steatosis seen in NAFLD is macrovesicular. In adults, similar histologic findings can be found in a number of conditions . The spectrum of abnormalities varies from simple bland steatosis to NASH, in which steatosis is associated with mixed inflammatory cell infiltration and liver injury. Cell injury is manifested by hepatocyte ballooning and by Mallory hyaline and acidophil bodies.

Despite the advantages of liver biopsy, its overall role in the evaluation of patients with NAFLD is unsettled, in large measure because of its risks and poor patient acceptance. In patients with risk factors for NAFLD (ie, metabolic syndrome), 3 to 6 months are often allowed for a trial of weight loss and for possible improvements in imaging studies and biochemical markers of liver disease. In the subset of patients most likely to have NASH or advanced disease (those older than 45 years, significant obesity, type 2 diabetes, multiple components of metabolic syndrome, low platelets, low albumin, AST/ALT ratio ≥1, evidence of portal hypertension) and in those with an unclear diagnosis, a liver biopsy should be considered earlier . A repeat liver biopsy in patients with NASH in 3-5 years should be considered to monitor disease progression.

Because of the important limitations of the currently available noninvasive and invasive tests, recent efforts have focused on identifying potential novel noninvasive biomarkers for NASH and assessment of fibrosis.

Treatment

The goal of treatment is to improve steatosis and prevent the development of fibrosis, which can lead to cirrhosis and its complications. Because the prognosis of NASH depends on risk factors (eg, obesity, insulin resistance, type 2 diabetes), these conditions have been the focus of treatment. Treatment proposed for NAFLD has been based on the 2-insult hypothesis; the first being

1. fatty liver infiltration (linked to obesity and insulin resistance)
2. oxidative stress. Patients should avoid alcohol and other hepatotoxins.

Treatment of Obesity

Weight reduction has been widely studied in adults with NASH and has been shown to improve not only the biochemical results but also the histology. A review of 3 randomized controlled trials on weight reduction through lifestyle and pharmacologic intervention suggested that weight loss is safe and can improve histologic parameters of NASH.

Slow, consistent weight loss through a diet designed to produce a caloric deficit of 500 to1000 kcal/day is advised. Reduction of dietary carbohydrates, in particular dietary fructose, is the most beneficial and has been found to improve the lipid profile in overweight patients. High- to moderate-intensity exercise (30 minutes, 3 to 5 times a week) has also been advocated to reduce the risk of comorbidities associated with obesity.

However, more realistically, patients should be encouraged to incorporate moderate activity into everyday life (eg, climbing stairs, walking instead of driving).

Pharmacologic treatment of obesity in NASH is still experimental. Several drugs have been studied, including

a. sibutramine, a serotonin reuptake inhibitor, and

b. orlistat, which reduces fat absorption.

Both of these have been shown to improve liver enzyme levels and sonographic signs of fatty liver. A meta-analysis of rimonabant, a cannabinoid-1-antagonist, showed that it is associated with increased adverse events and currently it cannot be recommended for NAFLD.

Finally, bariatric surgery is now suggested for patients with a BMI >40 kg/m^2, or for those with a BMI of >35 kg/m^2 and obesity-related comorbidities. Resolution in steatosis, but not of fibrosis, has been demonstrated. However, the safety of bariatric surgery in patients with cirrhosis is still under investigation. Randomized clinical trials are needed to determine if bariatric surgery is an appropriate therapy in NASH patients.

Insulin-Sensitizing Agents

NASH patients with diabetes are at higher risk of developing more-aggressive disease. Insulin-sensitizing agents have been tested in adults. Metformin, a biguanide oral anti-diabetic agent, lowers hepatic glucose production and promotes glucose uptake in the muscles. Studies on metformin have shown discrepant results.

Randomized controlled trials have shown improved serum liver enzymes and insulin resistance but inconsistent effects on liver histology. A large randomized trial in children with NASH did not show a sustained reduction in ALT or improvements in NAFLD activity score for histologic features in the liver.

Peroxisome proliferator-activated receptor gamma (PPARg) agonists (thioglitazones) have been shown to improve insulin resistance, a surrogate marker of fatty liver, and histology by promoting redistribution of triglycerides from the liver and muscle into proliferating adipocytes. Pioglitazone studies have shown conflicting results.

A recent phase 3, randomized, placebo-controlled, double blind clinical trial on the use of pioglitazone versus vitamin E versus placebo for the treatment of non-diabetic patients with NASH (PIVENS trial) showed no difference in the rate of improvement in NASH compared with placebo but it did show a reduction in aminotransferases and hepatic steatosis. Longer term trials suggest that long term therapy with thioglitazones are needed to maintain histologic improvement but would offer no additional histologic benefit.

Hepatotoxicity has been described with thioglitazones, and a more common side effect is paradoxical weight gain and fat redistribution. Although controversial, increased risk of cardiovascular events and bone loss with the use of rosiglitazone as well as of increased risk of heart failure with pioglitazone have been described.

Lipid-Lowering Agent

The literature concerning lipid-lowering medication and NAFLD is sparse. Reports have demonstrated improvement in transaminase levels with different classes of drugs, but there is a lack of histologic follow-up. Fibrates, in one randomized controlled trial, did not show any histologic benefit. Probucol, a lipophilic lipid lowering drug, has shown improvement in aminotransferases but it can also reduce high density lipoprotein levels. Although one of the most common side effect of statins is liver enzyme level elevation, evidence has pointed out that patients with elevated baseline transaminase levels (likely having NAFLD) who receive statin treatment do not have a higher incidence of liver enzyme level elevation or hepatotoxicity than liver disease control subjects who do not receive statins. Moreover, the clinical relevance of the current recommendation that liver biochemistry should be checked before and

periodically (usually 12 weeks) after treatment initiation has not been substantiated in the NAFLD population.

Antioxidants

Oxidative stress has been hypothesized to contribute to the progression of NAFLD to NASH and to worsen insulin resistance. For this reason, antioxidant treatment to reduce this stress and slow the progression of the disease has been studied. Several small trials in humans with NAFLD have supported an effect of tocopherol (vitamin E) on the improvement of transaminase levels but there have been discordant results in histologic improvement. The recent larger PIVENS trial showed that vitamin E (800 IU/d) led to an improvement in NASH compared with placebo as well as a reduction in aminotransferases. However, a controversial report has shown a mild increase in all-cause mortality in people taking high-dose vitamin E (≥400 IU/d) as a health supplement.

Hepato protective therapy

Several therapeutic agents believed to offer hepatocyte protection have been evaluated. Despite small adult studies suggesting a role of ursodeoxycholic acid in the improvement of NASH, a large, randomized, placebo-controlled trial has demonstrated no benefits from ursodeoxycholic acid over placebo on liver biochemistry and histology. Pentoxifylline inhibits a number of proinflammatory cytokines and may have hepatoprotective effects. One small randomized study showed improvement in histologic features of NASH when compared with placebo. Betaine and N-acetylcysteine have shown promising effects, but larger trials are needed.

Other Agents

The renin-angiotensin system may induce fibrosis in NAFLD. Angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers (ARBs) can improve insulin sensitivity. ARBs, in small studies including a randomized controlled trial, have shown improvement in histologic inflammation and fibrosis. Monounsaturated fatty acid intake improves cardiovascular risk and lipid profiles. Polyunsaturated fatty acids, studied in 3 randomized controlled trials, have been shown to improve biochemical and ultrasound features of liver steatosis (a phase II trial is underway).

In a randomized controlled trial, L-carnitine was found to improve steatosis, NAFLD histologic activity score and aminotransferases. Pilot studies based on the theory that NAFLD may be linked to small bowel bacterial overgrowth have shown some promise with the use of probiotics and prebiotics. An inverse association between coffee consumption and severity of fibrosis has been seen in multiple studies. Thus regular coffee consumption may be reasonable to recommend patients with NASH. Further advances in understanding the pathogenesis of NAFLD, such as induction of toll-like receptors leading to

proinflammatory and profibrogenic cytokines which contribute to NASH, may also help to provide new therapeutic options for NASH.

Practice Guidelines

Emerging data from recent trials have suggested that weight loss through lifestyle modifications, as well as several insulin-sensitizing, antioxidants, hepatoprotective medications and others, may be of benefit in patients with NAFLD (Table 3). In 2010, the Italian Association for the Study of the Liver and in 2012 the American Association for the Study of Liver Diseases in conjunction with the American College of Gastroenterology and the American Gastroenterological Association published evidence-based practice guidelines for the diagnosis and management of NAFLD. Both guidelines endorse lifestyle changes. A 3% to 4% loss in body weight likely improves steatosis, and weight of loss up to 10% may improve necro-inflammation. This can be achieved with a hypocaloric diet alone or in conjunction with exercise. Anti-obesity drugs are currently not recommended. Bariatric surgery in the appropriate individual may be useful to control obesity but the guidelines indicate that bariatric surgery is not yet an established option for the treatment of NASH.

Vitamin E is considered a first-line therapy in biopsy proven NASH in the practice guidelines although it is not advised in patients with diabetes or cirrhosis. Pioglitazone can be used to treat steatohepatitis in biopsy-proven NASH but long-term safety has not been established and it's use in a NASH population with diabetes has not been studied. Metformin, ursodeoxycholic acid, and omega-3 fatty acids are not recommended. Statins are deemed safe to use to treat dyslipidemia but are not currently recommended to treat NASH specifically. Further studies are needed for other therapies before they can be formally recommended.

Table 3.

Therapeutic approaches for nonalcoholic fatty liver disease

Weight Loss
Caloric restriction, exercise*
Sibutramine, orlistat
Weight-reduction surgery
Insulin-Sensitizing Agents
Metformin
Peroxisome proliferator-activated receptor gamma agonists (thiazolidinedione, rosiglitazone, **pioglitazone***)
Lipid-Lowering Drugs
Fibrates (gemfibrozil)

Fish oil
Antioxidants N-acetylcysteine **Vitamin E*** Betaine Pentoxifylline
Other Agents Angiotensin-converting enzyme inhibitors Angiotensin-receptor blockers Monounsaturated fatty acids Polyunsaturated fatty acids

.

Liver transplanatation

In patients with decompensated NAFLD cirrhosis, liver transplantation should be considered. Coexisting conditions (eg, morbid obesity, severe complications of diabetes, cardiac disease) and fear of intraoperative and post-transplantation complications, may preclude transplantation candidacy in these patients. A thorough pretransplantation evaluation, as well as better weight and metabolic derangement control, may be necessary. Following transplant, most patients have persistent metabolic syndrome, with long-term implications. Moreover, NAFLD has been shown to recur in the liver allograft, with a possible rapid progression to steatohepatitis and cirrhosis.

Prevention and Screening

More than 50 million Americans have been estimated to have the metabolic syndrome, and 80% of them probably have NAFLD. Furthermore, about one-third of the US population suffering from type 2 diabetes mellitus has fatty liver. The prevalence of NAFLD in the US seems to be substantially greater than the 2% prevalence of hepatitis C virus infection and is believed to be increasing. Given such a high prevalence, the American Gastroenterological Association Technical Review on Nonalcoholic Fatty Liver Disease, published in 2002, stated that "physicians should actively check for the

presence of NAFLD in those who are overweight and/or diabetic." Screening is complicated by the fact that the accuracy of noninvasive diagnostic tools remains poor and, apart from weight loss, there is no clearly established treatment for NAFLD. Basic laboratory evaluation of liver enzyme levels might point to the diagnosis but cannot rule out NAFLD if test results are normal, and imaging techniques have poor sensitivity for low-grade steatosis. Moreover, because these tests do not differentiate simple steatosis from NASH, a liver biopsy must be discussed with the patient if the suspicion of NASH is strong. Therefore, although generalized screening for fatty liver in all at-risk patients may be difficult and is not recommended by the practice guidelines, it is certainly warranted to look for and actively manage the metabolic syndrome (obesity, diabetes, hyperlipidemia, and hypertension). Prevention of obesity and its complications is now a major public health goal.

Summary

- Nonalcoholic fatty liver disease (NAFLD), a condition associated with obesity and diabetes, is increasingly being recognized in the Western population.

- Simple fatty liver is the most common form of NAFLD and seems to be a benign condition. In contrast, nonalcoholic steatohepatitis can progress to advanced fibrosis and cirrhosis.
- The diagnosis is often made after an incidental finding of elevated liver enzyme levels or due to the clinician's suspicion regarding a patient with obesity or diabetes. Laboratory results or imaging examinations can confirm the diagnosis. However, at present, only a liver biopsy can differentiate simple steatosis from NASH.
- Practice guidelines recommend weight loss, vitamin E, and pioglitazone for NASH. Other therapies require further investigation before they can be recommended.

Conclusions

NAFLD affects a substantial portion of the general population and is associated with metabolic syndrome, which includes obesity, insulin resistance, hyperlipidemia, and hypertension. Patients with NAFLD not only frequently suffer from insulin resistance but also have increased overall mortality.

Although simple fatty liver seems to be a benign condition, it can progress to NASH and ultimately to cirrhosis in some patients. Because of the consequences of the disease, we emphasize the importance of the detection of NAFLD in high-risk groups, including obese patients, as well as those with evidence of insulin resistance or other components of metabolic syndrome.

Screening and surveillance methods should be applied more uniformly from center to center, and reliable noninvasive techniques are needed to diagnose NAFLD and the detection of progressive liver disease.

The diagnosis of NAFLD should prompt management of metabolic risk factors. Weight loss regimens are believed to be helpful, and numerous drugs have been investigated in small studies. Large randomized clinical trials are necessary to determine the real benefit of these agents.

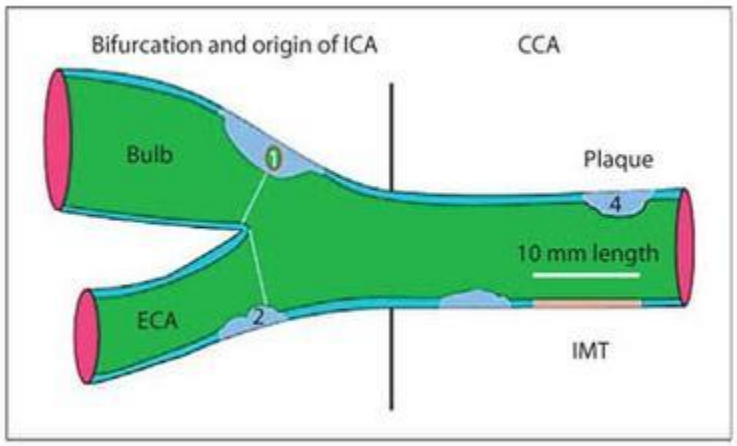
Finally, studies on the pathogenesis of NAFLD may not only improve our understanding of the mechanisms involved in NAFLD progression but also may lead to novel therapeutic strategies to treat this condition.

CAROTID INTIMA MEDIA THICKNESS

CIMT is a marker of subclinical atherosclerosis. CIMT of > 0.9mm or over the 75 th percentile should be considered as abnormal

Carotid ultrasound is the method of choice

B mode ultrasonagraphy is used. It s non invasive , easy, cheap, reproducible, sensitive, widely available.



CIMT is measured in the common carotid , just before the bifurcation .

CIMT is measured between lumen - intima and media – adventitia.

In the latest ESH/ESC hypertension guidelines (2013) carotid IMT > 0.9 mm is considered as marker of asymptomatic organ damage,

MATERIALS AND METHODS

STUDY POPULATION:

This study will be conducted between June 2016 to November 2016, among Patients with non alcoholic fatty liver who are admitted in General Medicine Department Of Government Rajaji Hospital, Madurai and equal number of age matched controls.

Inclusion criteria:

Sonographically proven fatty liver.

Age – adults > 30

Gender – both male and female

Non alcoholic or alcoholic with < 20g/day consumption

Exclusion criteria:

1. Patients who have problems for abdominal ultrasonography,
2. Those who are using steroid in diseases such as bronchial asthma, rheumatoid arthritis and Intestinal Bowel Disease (IBD) and
3. Those who are being treated with drugs affecting laboratory results, for example, aspirin, statins, fibrates and metformin,

4. those who have a history of liver disorders such as HBV or HCV, infection
5. Those who are consuming more than 20gm/ day of alcohol were excluded

METHOD:

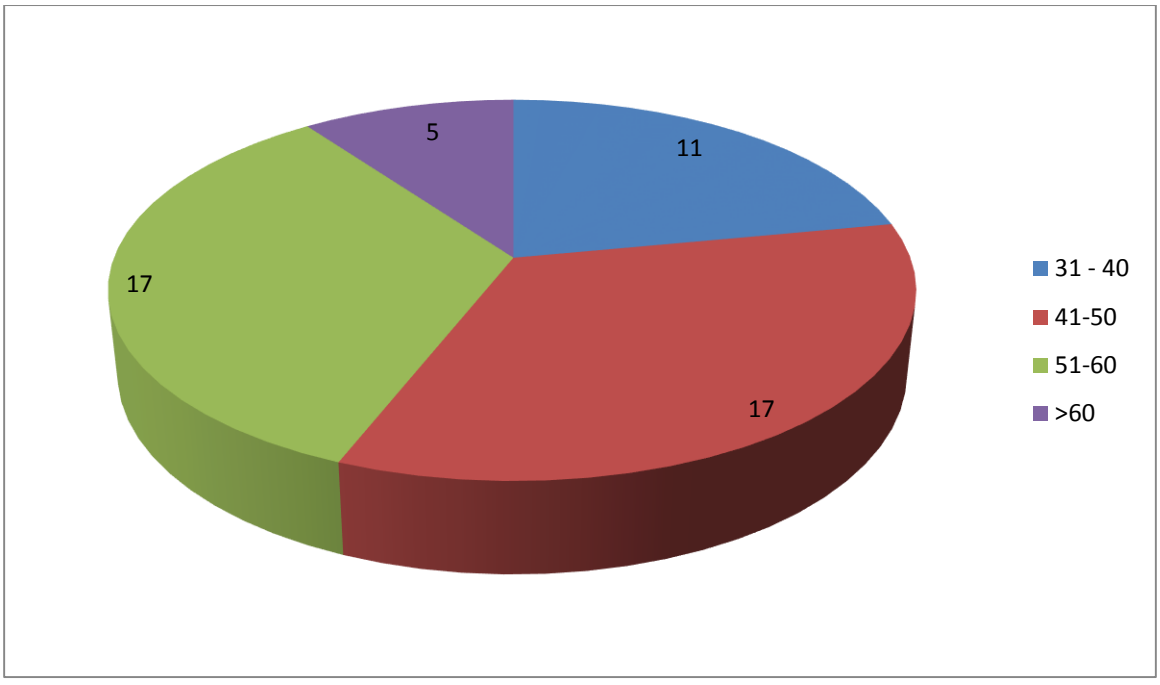
Fifty patients with NAFLD confirmed on abdominal ultrasound and 50 controls with normal liver parenchyma satisfying the inclusion and exclusion criteria are evaluated with

1. Complete history regarding presenting complaints, drug history, jaundice, and specific illness
2. h/o alcoholism and quantity
3. general examination inclulding BMI
4. systemic examination
5. routine blood investigation including FBS, lipid profile, viral markers for hepatitis virus b and c.
6. carotid artery doppler for measurement of CIMT and detection of atherosclerotic plaque
7. opthal examination for any associated fundus changes

RESULTS AND INTERPRETATION

AGE DISTRIBUTION AMONG NAFLD

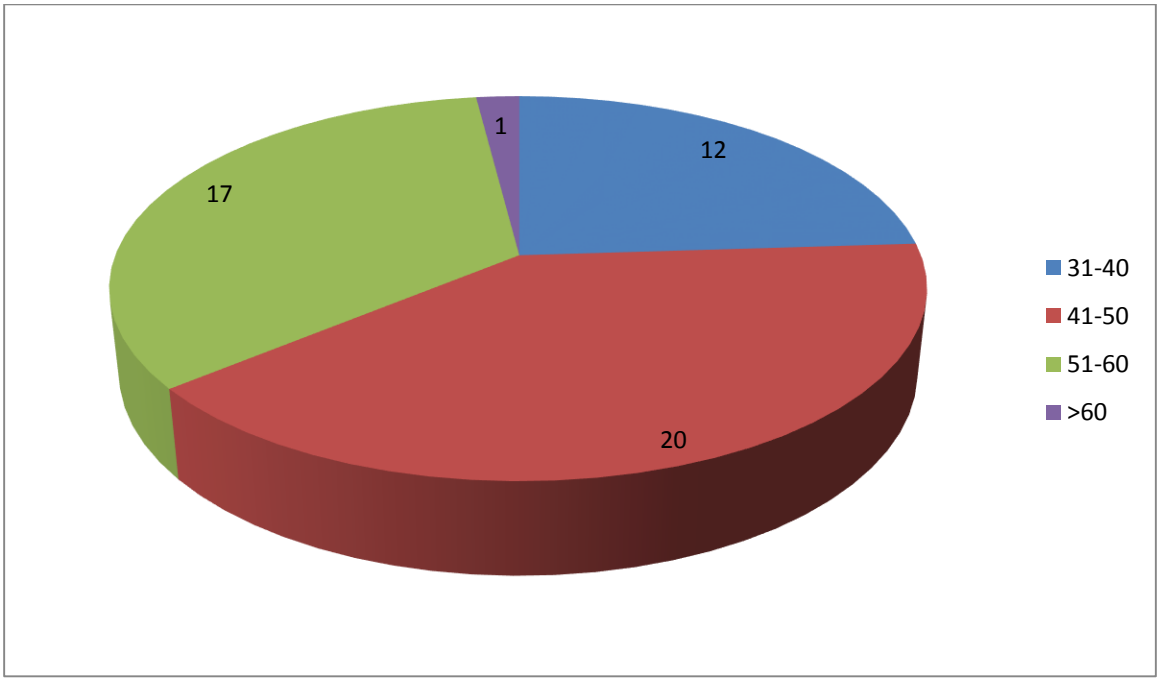
AGE	NAFLD	PERCENTAGE
31 – 40	11	22%
41- 50	17	34%
51 – 60	17	34%
➢ 60	5	10%
TOTAL	50	100%



Among NAFLD patients, most of them around 41 – 60 age group.

AGE DISTRIBUTION AMONG CONTROL

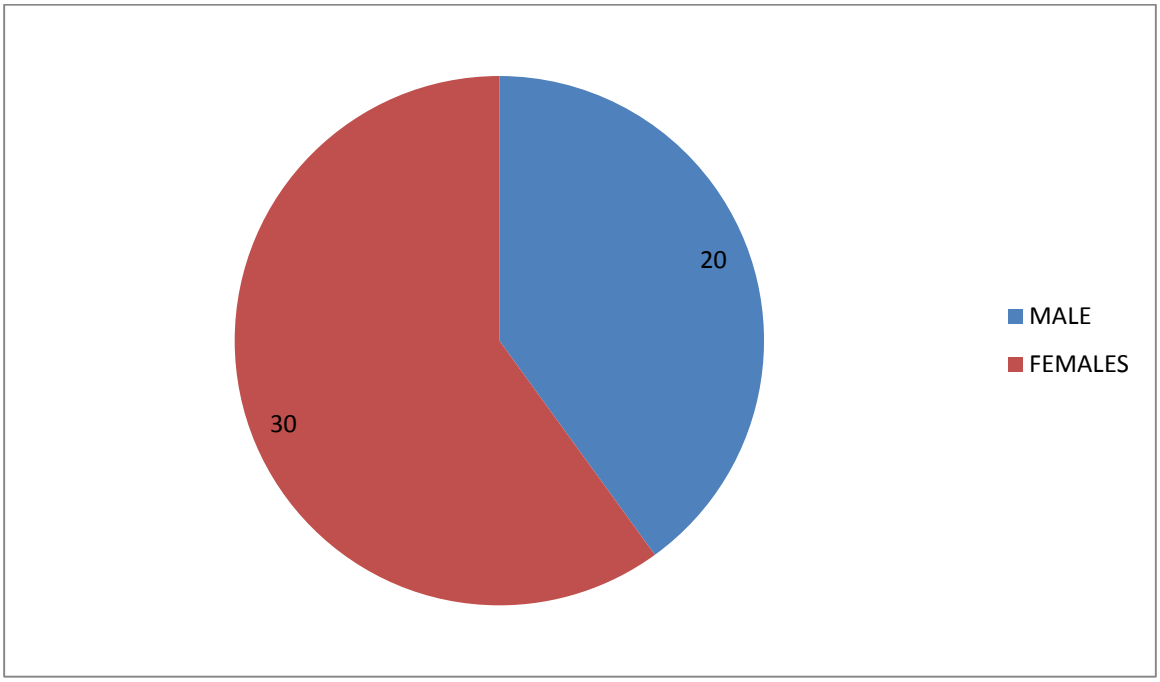
AGE	CONTROL	PERCENTAGE
31 – 40	12	24%
41- 50	20	40%
51 – 60	17	34%
➢ 60	1	2%
TOTAL	50	100%



Among control, most of the them in 41 – 50 age group

GENDER DISTRIBTUION IN NAFLD PATIENTS

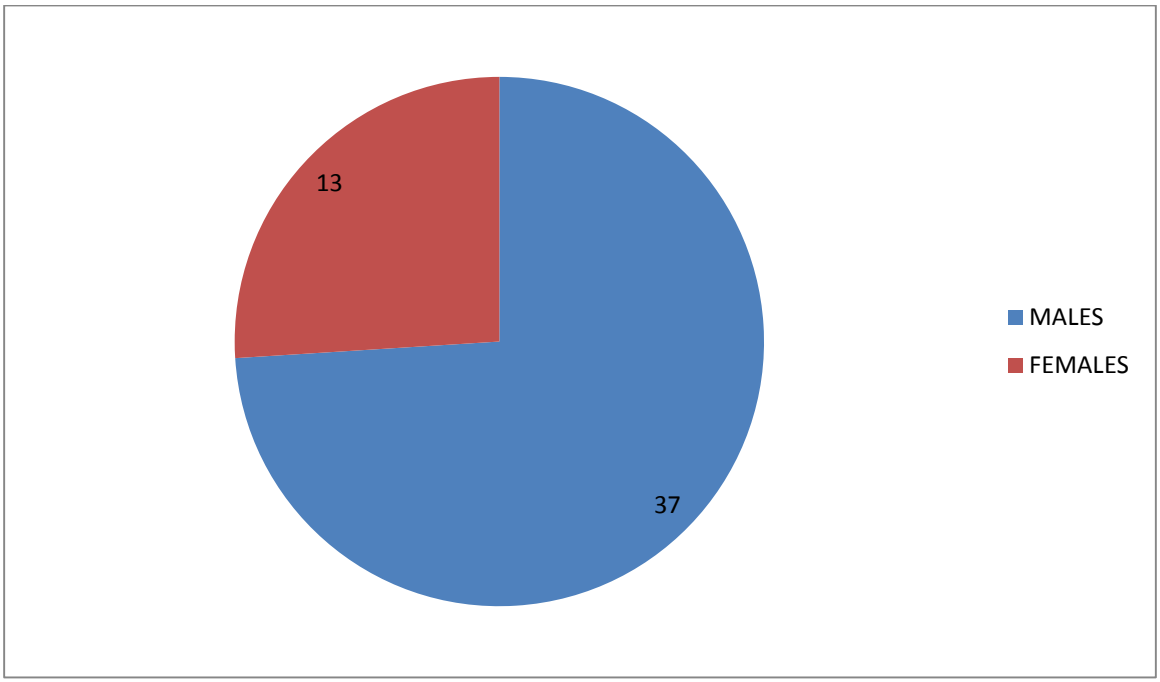
GENDER	NUMBER OF PATIENTS	PERCENTAGE
MALE	20	40%
FEMALE	30	60%
TOTAL	50	100



In this , among NAFLD patients, 60% were females and 40% males

GENDER DISTRIBUTION IN CONTROLS

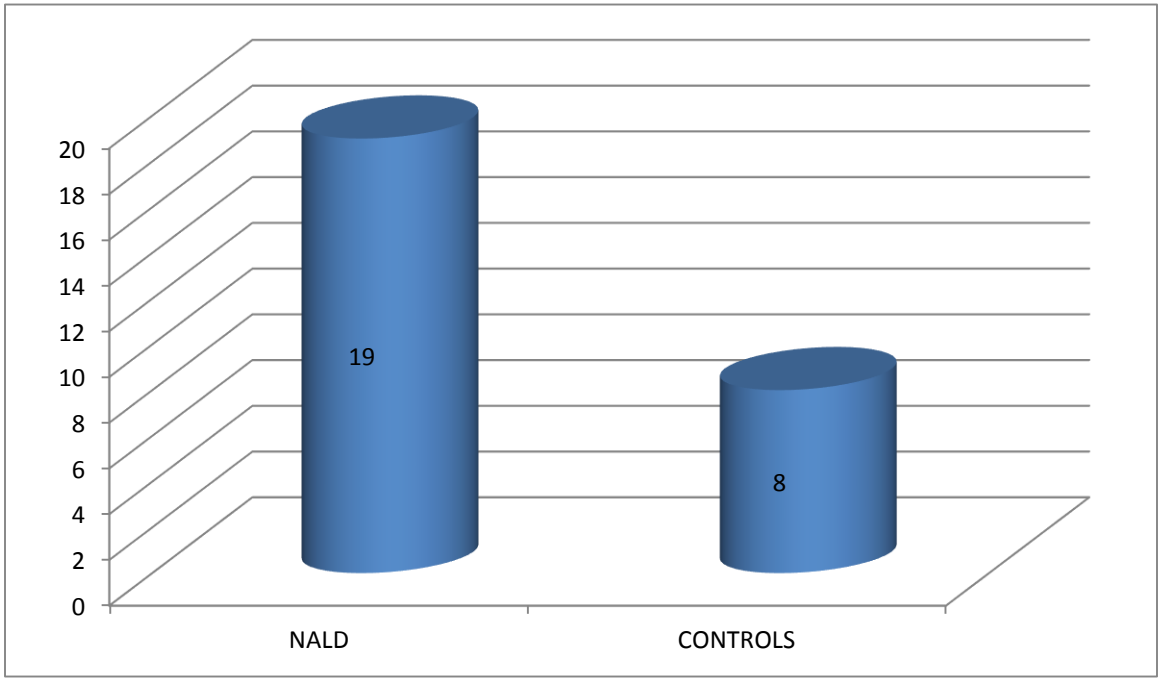
GENDER	NUMBER OF CONTROLS	PERCENTAGE
MALE	37	74%
FEMALE	13	26%
TOTAL	50	100



In this study, among controls 74% were males and 26% were females.

DISTRIBUTION OF DIABETES MELLITUS IN NAFLD PATIENTS AND CONTROLS

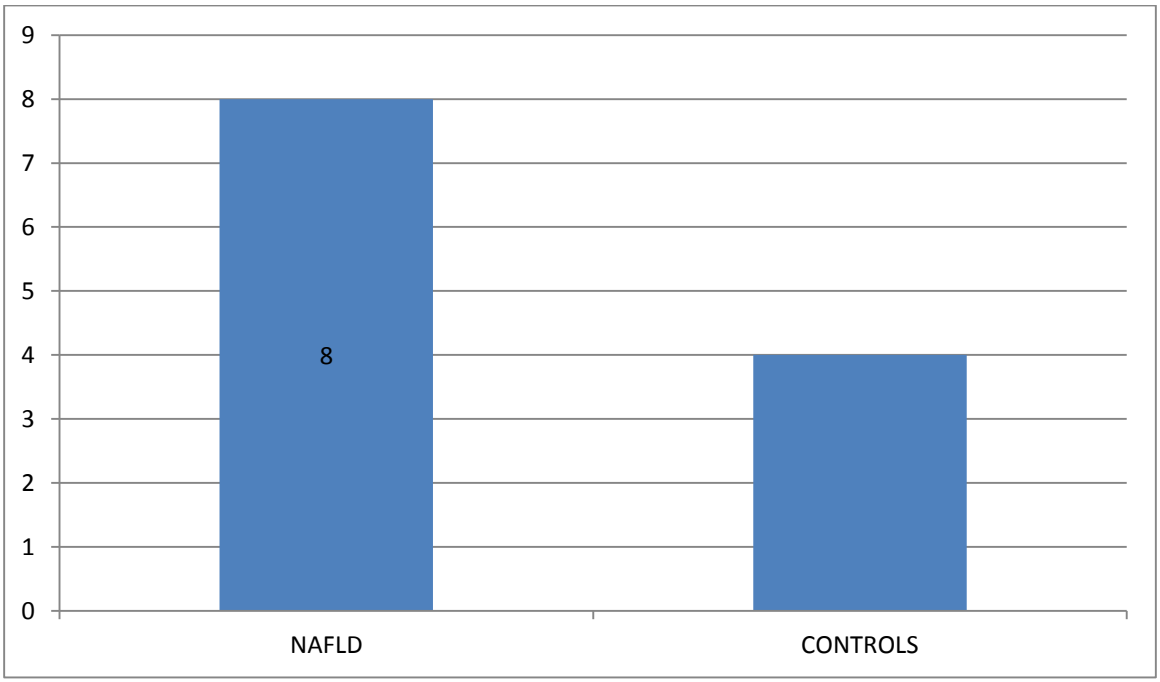
	DIABETES	PERCENTAGE
NAFLD	19	38%
CONTROLS	8	16%
TOTAL	27	54%



In NAFLD patients, 38% were diabetes mellitus and 16 % were diabetes among control

DISTRIBUTION OF OBESITY IN NAFLD PATIENTS AND CONTROLS

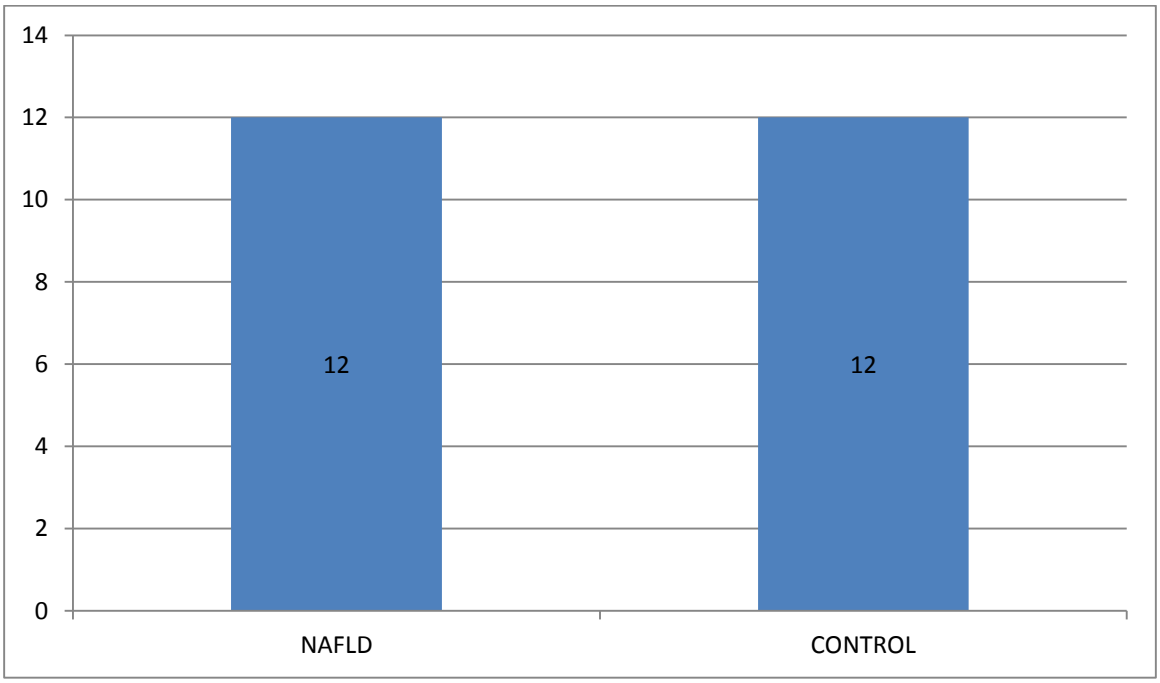
	OBESITY BMI >30	PERCENTAGE
NAFLD	8	16%
CONTROLS	4	8%
TOTAL	12	24%



Among NAFLD patients 16% were obese and among control 8% were obese.

DISTRIBUTION OF HYPERTENSION IN NAFLD AND CONTROLS

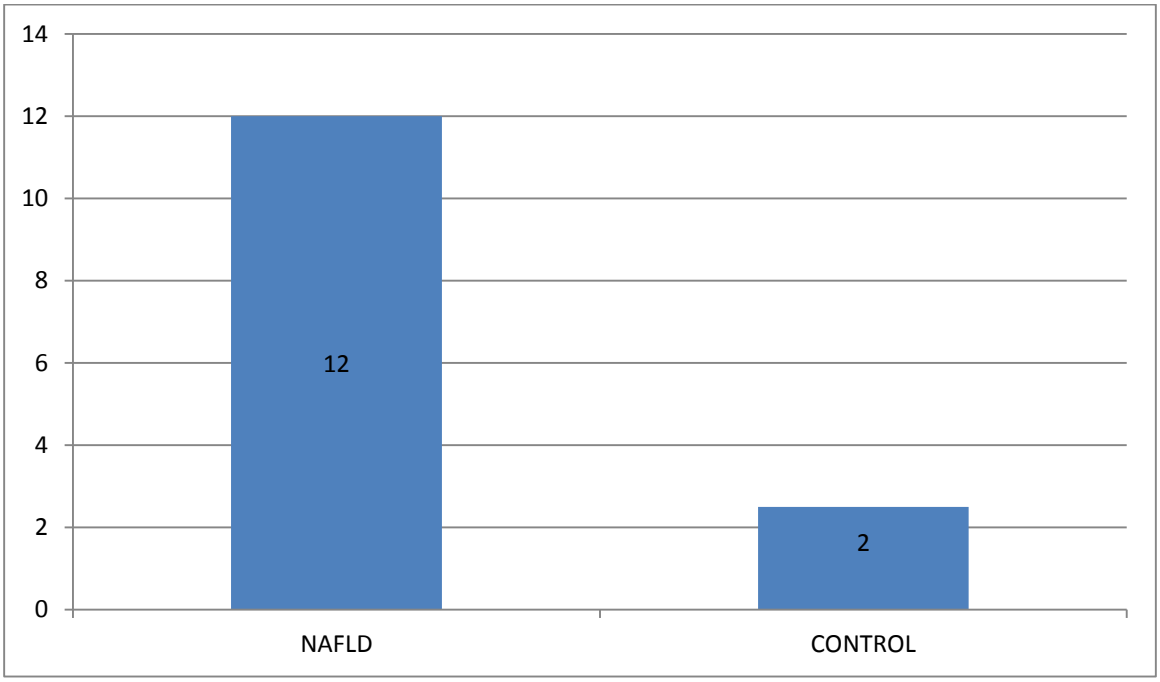
	HYPERTENSION	PERCENTAGE
NAFLD	12	24%
CONTROLS	12	24%
TOTAL	24	48%



Hypertensive patients are equal in number both in NAFLD and control.

DISTRIBUTION OF RETINAL ARTERY CHANGES IN NAFLD AND CONTROL

	RETINAL ARTERY CHANGES	PERCENTAGE
NAFLD	12	24%
CONTROLS	2	4%
TOTAL	14	28%

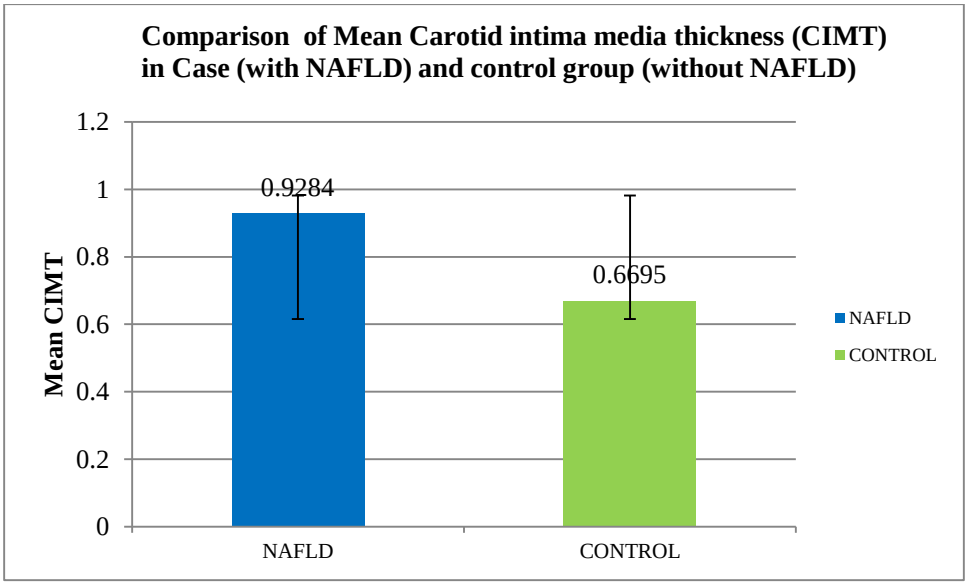


Among NAFLD patients, retinal artery changes are observed in 24% of the patients,

Among control, retinal artery changes observed only in 4% of the patients

COMPARISON OF CAROTID INTIMA MEDIA THICKNESS IN NAFLD PATIENTS AND NORMAL INDIVIDUALS

	RIGHT Carotid Intima Media Thickness	LEFT Carotid Intima Media Thickness	MEAN
NAFLD	0.9284 mm	0.9284mm	0.9284mm
CONTROLS	0.667mm	0.672mm	0.6695mm

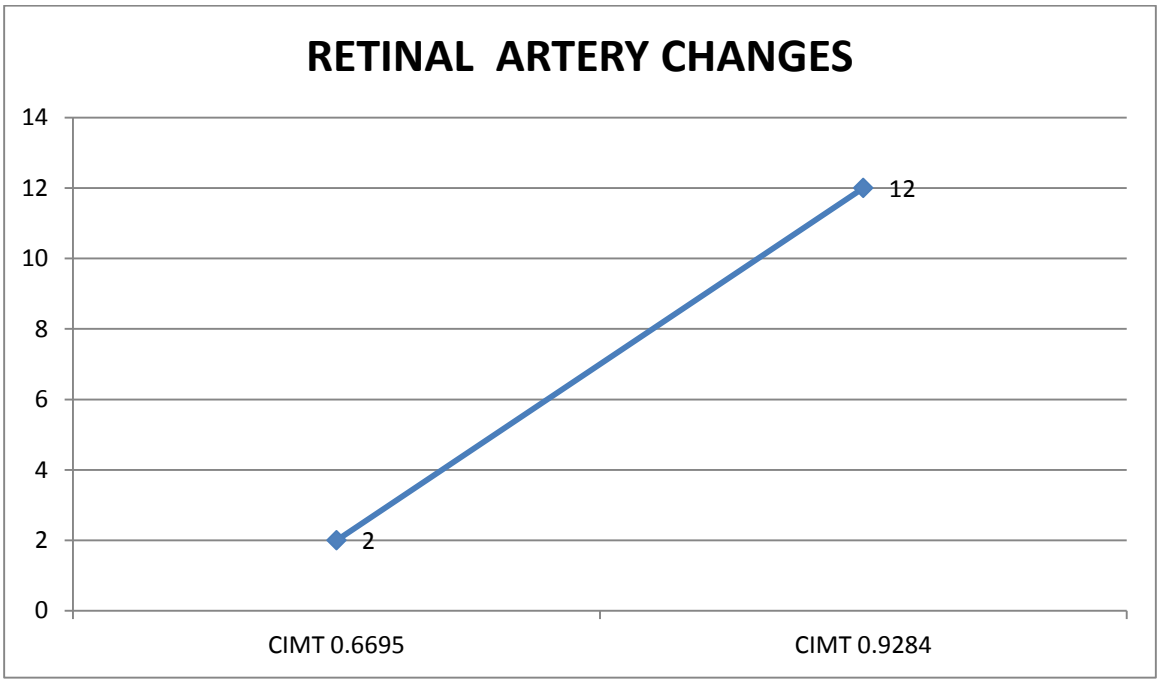


Mean carotid intima media thickness among NAFLD patients – 0.9284mm

Mean carotid intima media thickness among control – 0.6695mm

Association of mean carotid intima media thickness and retinal artery changes in NAFLD and control group

Mean CIMT	Retinal artery changes
0.9284 mm	12
0.6695 mm	2



In our study, it s clear that, increase in CIMT cause increase in retinal artery changes.

The collected data were subjected to statistical analysis using Statistical package for Social sciences [SPSS version 19.0 (SPSS Inc., Chicago, IL, USA)]. Categorical data were presented as numbers and percentages, whereas continuous data were expressed as mean and standard deviation (SD) or median and inter quartile range.

The continuous data was assessed for normality by Shapiro-wilk test. The pattern of distribution of each variable was found to be in **non normal distribution** thus non-parametric **Mann-Whitney U test** was indicated as appropriate test.

STASTICAL ANALYSIS

DESCRIPTIVES

	Subjects			Statistic	Std. Error
AGE	control	Mean		46.94	1.096
		95% Confidence Interval for Mean	Lower Bound	44.74	
			Upper Bound	49.14	
		Median		45.00	
		Std. Deviation		7.747	
		Interquartile Range		14	
	cases	Mean		47.82	1.342
		95% Confidence Interval for Mean	Lower Bound	45.12	
			Upper Bound	50.52	
		Median		45.00	
		Std. Deviation		9.486	

		Interquartile Range		11	
BMI_values	control	Mean		24.700	.4766
		95% Confidence Interval for Mean	Lower Bound	23.742	
			Upper Bound	25.658	
		Median		24.000	
		Std. Deviation		3.3700	
		Interquartile Range		5.2	
	cases	Mean		26.730	.5794
		95% Confidence Interval for Mean	Lower Bound	25.566	
			Upper Bound	27.894	
		Median		27.000	
		Std. Deviation		4.0973	
		Interquartile Range		4.6	
FBS	control	Mean		116.58	3.209
		95% Confidence Interval for Mean	Lower Bound	110.13	
			Upper Bound	123.03	
		Median		109.50	

		Std. Deviation		22.688	
		Interquartile Range		10	
	cases	Mean		122.02	2.933
		95% Confidence Interval for Mean	Lower Bound	116.13	
			Upper Bound	127.91	
		Median		110.00	
		Std. Deviation		20.739	
		Interquartile Range		28	
TGL	control	Mean		136.04	.935
		95% Confidence Interval for Mean	Lower Bound	134.16	
			Upper Bound	137.92	
		Median		138.00	
		Std. Deviation		6.608	
		Interquartile Range		10	
	cases	Mean		137.14	2.130
		95% Confidence Interval for Mean	Lower Bound	132.86	
			Upper Bound	141.42	

		Median		136.00	
		Std. Deviation		15.062	
		Interquartile Range		12	
HDL	control	Mean		49.58	.852
		95% Confidence Interval for Mean	Lower Bound	47.87	
			Upper Bound	51.29	
		Median		46.50	
		Std. Deviation		6.024	
		Interquartile Range		12	
	cases	Mean		45.08	.719
		95% Confidence Interval for Mean	Lower Bound	43.63	
			Upper Bound	46.53	
		Median		44.00	
		Std. Deviation		5.086	
		Interquartile Range		3	
R_CIMT	control	Mean		.667000	.0161327
		95% Confidence	Lower Bound	.634580	

		Interval for Mean	Upper Bound	.699420	
		Median		.650000	
		Std. Deviation		.1140757	
		Interquartile Range		.1675	
	cases	Mean		.928400	.0093650
		95% Confidence Interval for Mean	Lower Bound	.909580	
			Upper Bound	.947220	
		Median		.940000	
		Std. Deviation		.0662204	
		Interquartile Range		.0800	
L_CIMT	control	Mean		.672000	.0157428
		95% Confidence Interval for Mean	Lower Bound	.640364	
			Upper Bound	.703636	
		Median		.660000	
		Std. Deviation		.1113186	
		Interquartile Range		.1475	
	cases	Mean		.928400	.0095506

	95% Confidence Interval for Mean	Lower Bound	.909207
		Upper Bound	.947593
	Median		.935000
	Std. Deviation		.0675326
	Interquartile Range		.0825

Tests of Normality

	Subjects	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
		Statistic	df	Sig.	Statistic	Df	Sig.
AGE	control	.123	50	.057	.945	50	.022
	cases	.163	50	.002	.913	50	.001
BMI_values	control	.182	50	.000	.918	50	.002
	cases	.158	50	.003	.954	50	.051
FBS	control	.340	50	.000	.709	50	.000
	cases	.279	50	.000	.839	50	.000
TGL	control	.155	50	.004	.924	50	.003
	cases	.205	50	.000	.928	50	.005
HDL	control	.224	50	.000	.851	50	.000

	cases	.208	50	.000	.901	50	.001
R_CIMT	control	.150	50	.007	.947	50	.026
	cases	.170	50	.001	.918	50	.002
L_CIMT	control	.162	50	.002	.950	50	.034
	cases	.151	50	.006	.926	50	.004

a. Lilliefors Significance Correction

The test statistics are shown in the above table. Here two tests for normality are run. For dataset small than 2000 elements, we use the ShapiroWilk test,

otherwise, the KolmogorovSmirnovtest is used. In our case, since we have only 100 elements, the ShapiroWilk test is used. This conclude that the data is in non normal distribution

NPar Tests

[DataSet1]

Descriptive Statistics

	N	Mean	Std. Deviation	Minimum	Maximum	Percentiles 25th	Percentiles 50th (Median)	Percentiles 75th
AGE	100	47.38	8.628	34	65	42.00	45.00	54.00
BMI_values	100	25.715	3.8692	19.0	37.0	23.000	25.000	28.000
R_CIMT	100	.797700	.1608303	.4500	1.1000	.650000	.835000	.940000
L_CIMT	100	.800200	.1580882	.4500	1.1000	.660000	.835000	.937500
FBS	100	119.30	21.797	95	180	107.25	110.00	130.00
TGL	100	136.59	11.585	108	186	129.25	137.50	140.00
HDL	100	47.33	5.990	35	60	43.00	45.00	53.75
Subjects	100	.50	.503	0	1	.00	.50	1.00

Mann-Whitney Test

Ranks

	Subjects	N	Mean Rank	Sum of Ranks
AGE	control	50	49.38	2469.00
	cases	50	51.62	2581.00
	Total	100		
BMI_values	control	50	42.87	2143.50
	cases	50	58.13	2906.50
	Total	100		
R_CIMT	control	50	26.67	1333.50
	cases	50	74.33	3716.50
	Total	100		
L_CIMT	control	50	26.87	1343.50
	cases	50	74.13	3706.50
	Total	100		

FBS	control	50	45.43	2271.50
	cases	50	55.57	2778.50
	Total	100		
TGL	control	50	51.80	2590.00
	cases	50	49.20	2460.00
	Total	100		
HDL	control	50	61.15	3057.50
	cases	50	39.85	1992.50
	Total	100		

Test Statistics[a]

	AGE	BMI_values	R_CIMT	L_CIMT	FBS	TGL	HDL
Mann-Whitney U	1.194E3	868.500	58.500	68.500	996.500	1.185E3	717.500
Wilcoxon W	2.469E3	2143.500	1.334E3	1.344E3	2.272E3	2.460E3	1.992E3
Z	-.388	-2.650	-8.234	-8.159	-1.755	-.450	-3.700
Asymp. Sig. (2-tailed)	.698	.008	.001	.001	.079	.653	.001

a. Grouping Variable: Subjects

To compare proportions, the **CHI-SQUARE TEST** was employed as appropriate.

Chi square test

SEX * Subjects

Crosstab

			Subjects		Total
			control	cases	
SEX	Male	Count	37	20	57
		% within SEX	64.9%	35.1%	100.0%
		% within Subjects	74.0%	40.0%	57.0%
		% of Total	37.0%	20.0%	57.0%
	Female	Count	13	30	43
		% within SEX	30.2%	69.8%	100.0%
		% within Subjects	26.0%	60.0%	43.0%
		% of Total	13.0%	30.0%	43.0%

Total	Count	50	50	100
	% within SEX	50.0%	50.0%	100.0%
	% within Subjects	100.0%	100.0%	100.0%
	% of Total	50.0%	50.0%	100.0%

Chi-Square Tests

	Value	Df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	11.791[a]	1	.001		
Continuity Correction[b]	10.445	1	.001		
Likelihood Ratio	12.056	1	.001		
Fisher's Exact Test				.001	.001
Linear-by-Linear Association	11.673	1	.001		
N of Valid Cases[b]	100				

a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 21.50.

Fundus * Subjects

Crosstab

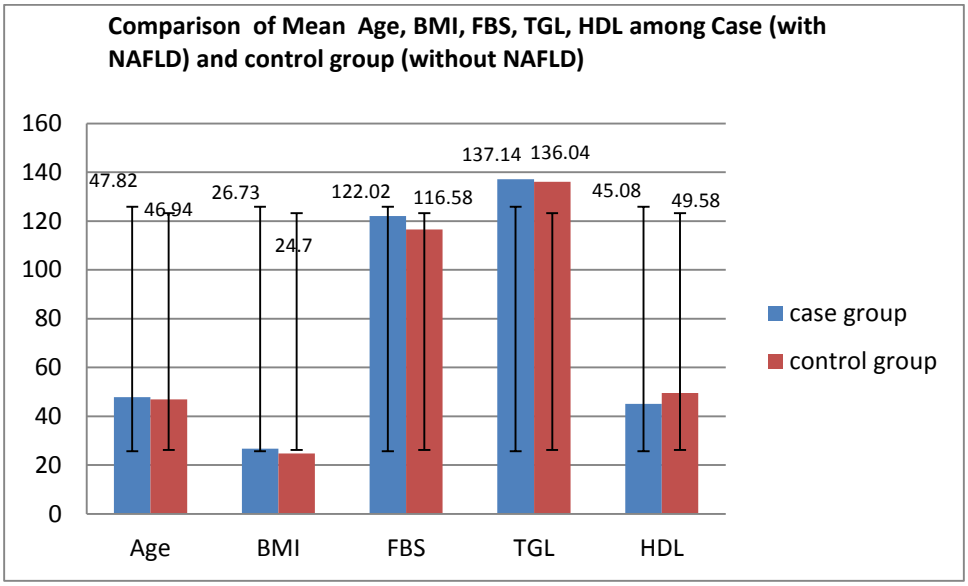
			Subjects		Total
			control	Cases	
Fundus	Normal	Count	48	38	86
		% within Fundus	55.8%	44.2%	100.0%
		% within Subjects	96.0%	76.0%	86.0%
		% of Total	48.0%	38.0%	86.0%
	Retinal artery changes	Count	2	12	14
		% within Fundus	14.3%	85.7%	100.0%
		% within Subjects	4.0%	24.0%	14.0%
		% of Total	2.0%	12.0%	14.0%
Total		Count	50	50	100

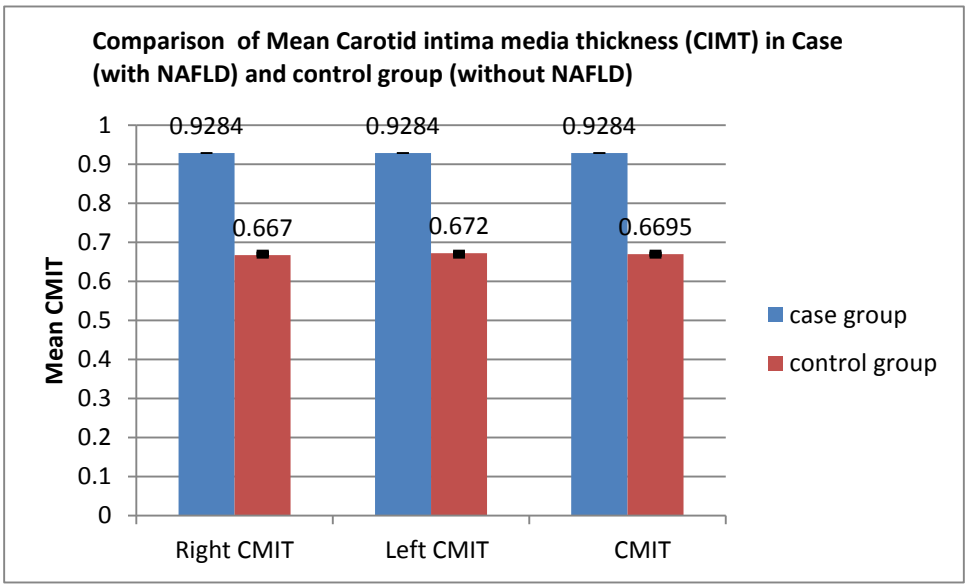
	% within Fundus	50.0%	50.0%	100.0%
	% within Subjects	100.0%	100.0%	100.0%
	% of Total	50.0%	50.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	8.306[a]	1	.004		
Continuity Correction[b]	6.728	1	.009		
Likelihood Ratio	9.090	1	.003		
Fisher's Exact Test				.008	.004
Linear-by-Linear Association	8.223	1	.004		
N of Valid Cases[b]	100				

a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 7.00.


Comparison of Mean Age, BMI, FBS, TGL, HDL among Case (with NAFLD) and control group (without NAFLD)
160
140
120
100
80
60
40
20
0
47.82
46.94
26.73
24.7
122.02
116.58
137.14
136.04
45.08
49.58
Age
BMI
FBS
TGL
HDL
case group
control group


Comparison of Mean Carotid intima media thickness (CIMT) in Case (with NAFLD) and control group (without NAFLD)
Mean CMIT
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.9284
0.667
0.9284
0.672
0.9284
0.6695
Right CMIT
Left CMIT
CMIT
case group
control group

RELATION OF NAFLD AND OTHER VARIABLES

1. There is strong association between carotid intima media thickness and NAFLD as pvalue is 0.001.
2. There is strong association between HDL and NAFLD as pvalue is 0.001
3. There is strong association between BMI and NAFLD as pvalue is 0.008
4. There is strong association between RETINAL ARTERY CHANGES and NAFLD as pvalue is 0.004
5. There is strong association between SEX and NAFLD as pvalue is 0.001. (as female prevalence is more in NAFLD patiens)

DISCUSSION

In this study, CIMT and retinal artery changes in NAFLD patients was compared with control, which showed that mean CIMT and retinal artery chages were significantly much more than the control group.

The results of our study are consistent with results of previous studies that are considered CIMT was associated with an increase in NAFLD and suggested it as the marker of early diagnosis of generalized atherosclerosis (Chiang *et al*., 2010; Guleria *et al*., 2013; Targher and Arcaro, 2007; Targher *et al*., 2008).

This actually means that type II diabetic patients with NAFLD are at greater risk of premature atherosclerosis and Coronary Vessels Disease (CVD).

As we stated before ultrasound screening method is a cheap and readily available. NAFLD estimates for up to one third of the total population and in the majority of patients with cardiovascular, metabolic and abdominal obesity, type II diabetes risk factors, can be seen. Our findings revealed NAFLD effect on CIMT was significant. In agreement with this finding, De Andrade *et al*. (2014) measured CIMT in a cross-sectional study on diabetes patients and showed that CIMT and CVD risk may be higher in those with a family history of type II diabetes. Besides, Nahandi *et al*. (2014) evaluated the effect of NAFLD on CIMT as a risk factor for atherosclerosis in patients with type II diabetes and reported that there is a

significant association between the presence of NAFLD and CIMT and its related atherosclerosis.

Mohammadi *et al*. (2011) examined patients with confirmed NAFLD for determination of CIMT and presence of carotid atherosclerotic plaque and reported that NAFLD with type II diabetes can be associated with increased CIMT and increased risk of atherosclerosis.

Moreover, Han *et al*. (2013) studied gender differences in the association between CIMT in healthy individuals and age-related increases in CIMT were correlated with a reduction in cardiac function only in women.

Our findings showed a considerable association between NAFLD and increased CIMT, in which this association is not affected by the severity of fatty liver. And also considerable association between retinal artery chages and NAFLD also observed

Considerable association between NAFLD and obesity and HDL levels are also observed

The internal carotid artery provides blood to the eye, therefore the pathology due to arteriosclerosis of these arteries may have a direct impact on retinal circulation and may coexist with retinal arteriosclerosis. So in our study , it s clear that , increase in carotid intima media thickness cause increased retinal artery changes.

Data explaining CIMT relates to future cardiovascular events are very few. Salonen and Salonen is the one of the few study available to date performed in a random sample (n=1257) of middle aged finnish men, reported that increase in **0.1mm of CIMT was associated with an 11% increase** in the risk of cardiovascular complication.

Hence all our NAFLD patients are treated with statins and other cardioprotective drugs, and also they are advised to follow up regularly once in every 6 months. They are advised to take treatment for NAFLD with insulin sensitizers.

So, immediate ultrasound screening and treatment for the patients with NAFLD are recommended to prevent CVD complications such as atherosclerosis considering early stages of fatty liver disease.

CONCLUSION

Non-Alcoholic Fatty Liver Disease (NAFLD) is one of the most common liver diseases reported all over the world. Carotid Intima Media Thickness (CIMT) is a useful tool for detection of sub-clinical atherosclerosis.

In our study, we found that, there is strong association between, NAFLD and

1. **Carotid intima media thickness**
2. **Retinal artery changes**

we also found significant association between NAFLD and body mass index and HDL levels.

So all patients with NAFLD should be investigated with carotid Doppler, and they all should treated with statins and other cardioprotective drugs to prevent cardiovascular complication.

They all should get treatment for obesity and with insulin sensitizers to prevent the progression of NAFLD.

This simple and non-invasive practice will help in early diagnosis of cardiovascular disease, especially in overt cases

LIMITATION OF THE STUDY

Since fatty liver is distributed in more number, our study with small n value , may not represent the whole population.

Patient may deny the alcohol history to avoid the social stigmata, that patient may falsely fall in NAFLD category.

Imaging studies like ultrasound and carotid intima media thickness may have inter observer variation

PROFORMA

Name:

Age / Sex:

IP no:

Occupation:

Presenting complaints:

Past History:

Risk factors:

Personal history

smoker/ nonsmoker

alcoholic : Duration: Quantity:

non alcoholic

General Examination

Consciousness, Pallor, icteric, Clubbing, Lymphadenopathy, hydration status

Vitals:

PR BP

Systemic examination:

CVS:

RS:

ABDOMEN:

CNS:

Laboratory investigations:

Complete blood count

Serum electrolytes

Renal function test

USG ABDOMEN	CAROTID DOPPLER	FUNDUS
	R	
	L	

LFT	LIPID PROFILE	VIRAL MARKERS
ALT	TGL	HIV
AST	TC	HBSAG
T.B.	LDL	HCV
	HDL	
	VLDL	

Diagnosis

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ABBREVIATION

1. NAFLD – non alcoholic fatty liver disease
2. CIMT – Carotid intima media thickness
3. BMI – body mass index
4. FBS – fasting blood sugar
5. HDL – high density lipoprotein
6. TG - triglyceride
7. CVD – carodiovascular diseases
8. HBV - hepatitis B virus
9. HCV – hepatitis C virus
10. SD – standard deviation
11. SPSS – stastical package for social sciences
12. EHA – European heart association
13. GGT – gamma glutamyl transpeptidase
14. AST – aspartate transminase
15. ALT – alanine transminase

MASTER CHART - NAFLD PATIENTS

NAME	AGE	SEX	BMI	BP	FBS	TGL	HDL	USG	R CAROTID	L CAROTID	FUNDUS
VEERAYAEE	35	F	23.5	120/80	108	135	43	GR II	0.83	0.83	NORMAL
SARAVANA KUMAR	34	M	27	130/85	110	123	44	GR I	0.94	0.95	NORMAL
KAVITHA	45	F	32	150/100	130	160	38	GR II	0.95	0.94	GRI
RANI	54	F	28	130/80	108	135	43	GRI	0.79	0.78	NORMAL
VEERAYAEE	54	F	28	120/80	110	134	54	GRII	0.87	0.86	NORMAL
ALAGAR SAMY	34	M	24	120/80	110	124	43	GRII	0.95	0.94	NORMAL
BOOPATHY	65	F	26	130/80	108	145	44	GRII	0.97	0.98	NORMAL
KANNAMAL	34	F	20	120/80	106	123	53	GRIII	0.98	0.98	NORMAL
RANJITHA	54	F	34	160/100	137	170	35	GRII	0.98	0.97	GRI
VELUTHAI	45	F	29	120/80	130	129	43	GRI	0.95	0.96	GRI
CHELLATHAL	56	F	34	130/90	120	159	45	GRII	0.94	0.93	GRII
SAMPATH KUMAR	54	M	24	130/80	180	140	46	GRI	1.1	1.1	NORMAL
SARANYA	43	F	28	130/80	160	137	43	GRI	0.87	0.88	NORMAL
PANJAVARNAM	45	F	28	120/80	107	139	54	GRI	0.99	0.99	NORMAL
KUMARI	65	F	24	120/80	110	108	46	GRII	0.93	0.93	NORMAL
XAVIER	34	M	23	110/70	102	110	50	GRIII	0.98	0.98	NORMAL
IRULAAYEE	45	F	23	120/80	145	130	51	GRII	0.72	0.72	NORMAL
RAJATHI	54	F	25	130/80	109	120	43	GRI	0.88	0.88	NORMAL

NALLAYAN	53	M	28	110/70	170	145	45	GRII	0.93	0.92	GRI
SREENIVASAGI	64	F	28	130/80	110	138	44	GRI	0.88	0.88	NORMAL
MATHI	45	M	27	120/80	130	128	43	GRI	0.97	0.97	NORMAL
DEEPIKA	43	F	28	120/80	108	129	53	GRI	0.88	0.88	NORMAL
DEVAKI	56	F	29	160/100	140	135	54	GRI	0.97	0.98	NORMAL
KANNAMAL	65	F	37	150/90	109	186	35	GRII	0.96	0.95	GRII
SUBRAMANI	45	M	28	120/80	98	124	42	GRI	0.94	0.95	NORMAL
BAAKIA	45	F	32	150/90	130	155	36	GRII	0.98	0.99	GRII
RAMAN	43	M	24	160/100	109	139	46	GRII	0.99	0.99	NORMAL
KALIYAMMAL	34	F	23	110/70	110	134	56	GRI	0.94	0.93	NORMAL
GURUNATHAN	54	M	26	120/80	140	120	44	GRIII	0.92	0.92	NORMAL
MADHAVAN	56	M	36	150/90	120	160	38	GRII	0.93	0.94	GRII
MADHU	54	F	22	130/80	140	127	43	GRI	0.84	0.84	NORMAL
MAHALAKSHMI	34	F	19	110/70	102	140	56	GRIII	1.1	1.1	NORMAL
MURUGAN	45	M	28	150/90	110	130	43	GRI	0.89	0.88	NORMAL
RAMANATHAN	56	M	28	120/80	108	140	44	GRII	0.78	0.78	NORMAL
MUTHAMMAL	65	F	28	130/70	100	120	45	GRI	0.94	0.95	NORMAL
KATHIRESAN	54	M	21	120/80	108	130	45	GRIII	0.92	0.92	NORMAL
PITCHIYAMMAL	45	F	21	160/100	130	140	46	GRI	0.98	0.98	NORMAL
RANJITHA	43	F	29	120/80	108	123	42	GRII	0.92	0.92	GRI
BALAMURUGAN	34	M	28	110/70	110	139	45	GRI	0.92	0.92	NORMAL
MAARIYAMMAL	54	F	27	130/85	136	139	43	GRII	0.89	0.89	NORMAL
INBARAJ	56	M	25	130/80	180	138	45	GRI	0.93	0.93	NORMAL
PAVITHRA	54	F	28	130/80	105	140	54	GRI	0.95	0.94	GRI

RAVIKUMAR	35	M	22	120/80	98	129	43	GRI	0.89	0.89	NORMAL
SREEJA	46	F	24	150/90	140	139	46	GRII	0.97	0.98	NORMAL
THANGA RAM	35	M	23	110/70	110	140	47	GRI	0.92	0.92	NORMAL
DEVI	45	F	31	140/90	140	156	44	GRII	0.94	0.94	GRI
KANDHASAMY	36	M	22	110/80	110	128	45	GRIII	0.89	0.89	NORMAL
CHANDRAKUMARI	56	F	23	160/100	156	145	43	GRII	0.92	0.91	NORMAL
NADUKAATTAN	45	M	27	120/80	120	130	43	GRI	0.97	0.98	NORMAL
SENTHIL	46	M	34	150/90	126	170	38	GRII	0.95	0.96	GRII

MASTER CHART – CONTROL GROUP

NAME	AGE	SEX	BMI	BP	FBS	TGL	HDL	USG	R CAROTID	L CAROTID	FUNDUS
VISWANATHAN	43	M	23	150/90	97	134	44	NORMAL	0.72	0.71	NORMAL
KUMAR	54	M	28	140/90	158	145	43	NORMAL	0.65	0.66	NORMAL
FATHIMA	34	F	22	110/80	109	130	56	NORMAL	0.54	0.55	NORMAL
RAVINDRAN	56	M	28	140/90	98	139	50	NORMAL	0.65	0.66	NORMAL
CHINNA DEVAR	45	M	24	110/80	108	140	45	NORMAL	0.78	0.79	NORMAL
MARY	36	F	23	120/80	112	130	54	NORMAL	0.87	0.88	NORMAL
BALA	56	M	23	140/90	180	128	57	NORMAL	0.65	0.66	NORMAL
MURALI	45	M	28	130/80	110	130	58	NORMAL	0.78	0.77	NORMAL

NERAI PANDI	34	M	22	110/80	103	140	45	NORMAL	0.65	0.66	NORMAL
KARPAGAM	54	F	23	150/90	98	129	50	NORMAL	0.56	0.57	NORMAL
RAMESH	45	M	24	140/90	110	134	46	NORMAL	0.78	0.77	NORMAL
VEERAPANDI	56	M	24	150/90	102	145	59	NORMAL	0.65	0.66	NORMAL
CHANDRAN	54	M	28	130/85	149	159	58	NORMAL	0.54	0.55	NORMAL
GOPAL	34	M	24	110/80	103	130	54	NORMAL	0.56	0.57	NORMAL
VALLI	45	F	29	140/90	110	129	56	NORMAL	0.91	0.91	GR I
MUTHUMANI	38	M	19	130/80	####	140	45	NORMAL	0.65	0.65	NORMAL
RAJA	37	M	23	110/80	106	138	43	NORMAL	0.45	0.46	NORMAL
MAYYEE	48	F	24	130/80	95	140	58	NORMAL	0.78	0.77	NORMAL
RAJATHI	41	F	24	140/90	103	139	59	NORMAL	0.64	0.65	NORMAL
MOHAN	54	M	28	150/90	110	134	43	NORMAL	0.65	0.66	NORMAL
MADHAVAN	58	M	26	130/85	156	140	42	NORMAL	0.45	0.45	NORMAL
KALIAPPAN	54	M	28	130/80	98	130	45	NORMAL	0.67	0.68	NORMAL
NATARAJAN	39	M	22	110/80	109	140	43	NORMAL	0.63	0.64	NORMAL
ISAKKI	48	M	26	120/80	110	134	50	NORMAL	0.67	0.68	NORMAL
JENIFFER	49	F	21	120/80	180	123	57	NORMAL	0.71	0.71	NORMAL
ALAGAR SAMY	59	M	34	150/90	140	145	43	NORMAL	0.78	0.77	NORMAL
KOOTHA PERUMAL	45	M	28	140/90	112	135	45	NORMAL	0.65	0.66	NORMAL
PARMASIVAM	42	M	22	160/100	109	134	46	NORMAL	0.54	0.55	NORMAL
MEENA	38	F	31	130/80	112	145	52	NORMAL	0.56	0.57	NORMAL
RANGAN	45	M	27	140/90	114	132	45	NORMAL	0.79	0.78	NORMAL
PANIYAN	38	M	22	110/80	112	126	56	NORMAL	0.65	0.65	NORMAL

JEYAPANDI	38	M	21	130/80	109	135	45	NORMAL	0.45	0.46	NORMAL
MUTHUSELVI	39	F	19	140/90	98	140	54	NORMAL	0.78	0.77	NORMAL
RAJANGAM	42	M	22	130/90	120	139	47	NORMAL	0.64	0.65	NORMAL
NARAYANAN	48	M	24	150/90	110	138	43	NORMAL	0.65	0.66	NORMAL
KALYANI	58	F	25	130/90	180	140	56	NORMAL	0.45	0.45	NORMAL
RAMACHANDRAN	59	M	34	140/90	108	139	45	NORMAL	0.67	0.68	NORMAL
MUNIYANDI	53	M	22	130/80	104	145	44	NORMAL	0.92	0.93	NORMAL
GOWTHAMI	57	F	31	140/90	102	128	60	NORMAL	0.67	0.68	NORMAL
KANNIYA	43	M	25	150/90	110	130	46	NORMAL	0.71	0.71	NORMAL
MARIYAPPAN	58	M	26	160/100	140	140	56	NORMAL	0.72	0.71	GRI
REVATHI	43	F	22	120/80	120	138	57	NORMAL	0.65	0.66	NORMAL
KALIMUTHU	51	M	25	110/80	112	128	43	NORMAL	0.54	0.55	NORMAL
DAVID	39	M	25	110/80	110	140	47	NORMAL	0.65	0.66	NORMAL
SETHU	43	M	23	140/90	106	129	44	NORMAL	0.78	0.79	NORMAL
VAIRAVAN	47	M	23	150/90	108	130	46	NORMAL	0.87	0.88	NORMAL
MUTHUSELVAM	49	M	23	160/100	98	140	56	NORMAL	0.65	0.66	NORMAL
SUBHASHINI	53	F	24	130/90	166	138	56	NORMAL	0.78	0.77	NORMAL
RAJAN	43	M	21	140/90	104	128	43	NORMAL	0.65	0.66	NORMAL
CHANDRU	60	M	22	150/90	102	140	44	NORMAL	0.56	0.57	NORMAL

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ETHICS COMMITTEE CERTIFICATE

Name of the Candidate	:	Dr.T.M.Prabhu
Course	:	PG in M.D., General Medicine
Period of Study	:	2014-2017
College	:	MADURAI MEDICAL COLLEGE
Research Topic	:	A study of carotid intima-media thickness and retinal vascular changes in patients with non alcoholic fatty liver disease
Ethical Committee as on	:	10.06.2016

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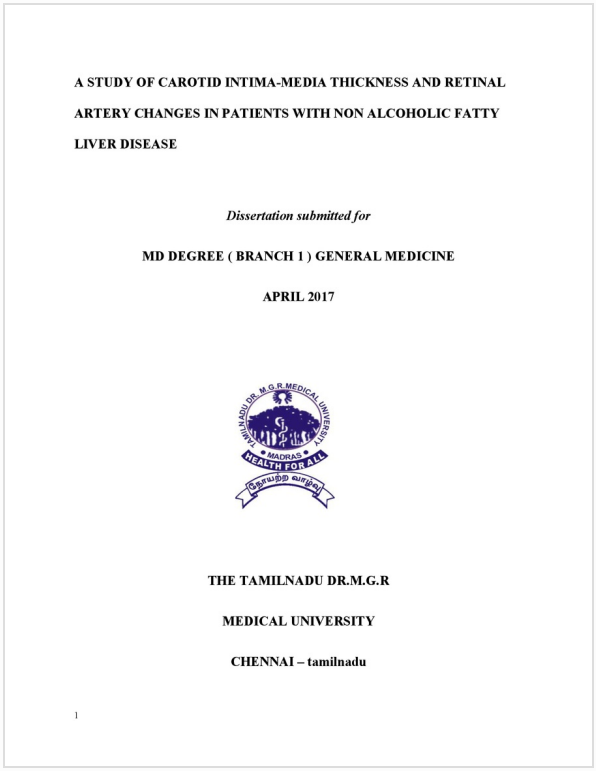

A STUDY OF CAROTID INTIMA-MEDIA THICKNESS AND RETINAL ARTERY CHANGES IN PATIENTS WITH NON ALCOHOLIC FATTY LIVER DISEASE

Dissertation submitted for

MD DEGREE (BRANCH 1) GENERAL MEDICINE

APRIL 2017

THE TAMILNADU DR.M.G.R

MEDICAL UNIVERSITY

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1

STUDY OF CAROTID INTIMA MEDIA THICKNESS AND RETINAL ARTERY CHANGES IN PATIENTS WITH NAFLD

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